GUIDELINES FOR THE ACUTE MEDICAL MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY IN INFANTS, CHILDREN, AND ADOLESCENTS

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Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents

Practice guidelines for physicians who treat children with brain trauma are long overdue. A significant barrier to producing guidelines has been the lack of data from well-designed, controlled studies that address each specific juncture of the acute treatment phase. Our goal with this document was to assimilate the scarce data that exist and present it within an evidence-based framework in order to provide treatment guidelines. With topics for which there were no evidence-based data, we worked as a group to achieve consensus and provided treatment options. To accomplish this, we assembled a multidisciplinary team of clinicians and researchers, keeping in mind that the presence of multiple perspectives would minimize bias. Although we recognize that this list is not complete, it represents a multidisciplinary group of clinicians and scientists with considerable expertise in key areas relevant to the project.

We consider this work a "document in progress" and are committed to its ongoing revision and to incorporating additional areas of expertise that may not currently be represented. It is our goal that these guidelines be used to distinguish important areas of research, so that future revisions will contain more substantial evidence.

A number of acknowledgments must be made. The template for our work has been the adult guidelines of the Brain Trauma Foundation. This previous work made important distinctions in treatment that we used to formulate pediatric topics. As such, we are indebted to the Brain Trauma Foundation for their organization and support for the adult severe head injury guidelines—and to the authors of that document. Due to the relatedness of the two documents, we have frequently referred to and quoted from the original adult document and its more recent revision (1, 2).

The International Brain Injury Association assembled the first working group for this project in March 2000 and provided additional funding for subsequent meetings of the research team. We also wish to thank Jansjörg Wyss (Chair and CEO), Tom Higgins (President, Spine), Steve Murray (President, Maxillofacial), and Paul Gordon (Group Manager of Programs) of Synthes USA for their generous, unrestricted contributions for meeting and administrative costs. The National Center for Medical Rehabilitation Research in the National Institute of Child Health and Human Development and National Institute of Neurologic Disorders and Stroke contributed the funds for joint supplemental publication of this document. We are indebted to Drs. Michael Weinrich and Mary Ellen Michel at these two institutes, respectively, for their assistance.

We wish to acknowledge the willingness of Dr. Joseph Parrillo, editor in chief of *Critical Care Medicine*, and Dr. Basil Pruitt, editor in chief of the *Journal of Trauma*, to partner with us in this important and unique triple supplement in the journals *Critical Care Medicine*, *Pediatric Critical Care Medicine*, and the *Journal of Trauma*. This was also facilitated through the efforts of John Ewers, publisher at Lippincott Williams and Wilkins, and Deborah McBride, Director of Publications at the Society of Critical Care Medicine. Simultaneously publishing this document as supplements in three journals is unique and will ensure dissemination to an international audience of more than 30,000 subscribers, crossing multiple disciplines.

One of the greatest challenges in producing an evidence-based document with multiple authors is the administrative management of the project. The expertise to meet this challenge was provided by personnel of the Evidence Based Practice Center of Oregon Health and Science University, and the project would not have succeeded without this resource.

Members of the research team belong to a number of important medical societies that have provided a background of support throughout this project. Included are the Society of Critical Care Medicine, the Sections of Neurotrauma and Critical Care and Pediatrics of the American Association of Neurologic Surgeons, the Congress of Neurologic Surgeons, the American Academy of Pediatrics, the American College of Emergency Physicians, and the World Federation of Pediatric Intensive and Critical Care Societies. Because of temporal constraints inherent in the preparation of this document, it was not possible to obtain formal endorsement by all of the relevant societies. We thank these societies along with the Child Neurology Society, the American Association for the Surgery of Trauma, the International Trauma Anesthesia and Critical Care Society, and the International Society for Pediatric Neurosurgery for important feedback and are especially grateful to those that gave expedited approval to the document.

Finally, and most sincerely, we thank each person who served as an investigator and coauthor on this project. We trust that the uncompensated time and absolute commitment over three years will result in improved outcomes for children who sustain traumatic brain injury.

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Chapter 1: Introduction

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A comparison of pediatric with adult trauma, using the National Pediatric Trauma Registry, indicates that a greater proportion of pediatric than adult trauma involves traumatic brain injury (TBI) (1). However, because of difficulty in evaluating treatments across age groups and developmental phases for children with TBI, little substantial research has been conducted to specify standard treatments for acute care as well as inpatient and outpatient rehabilitation (2). The persistence of some federal funding agencies to devote their resources exclusively to studies of adult populations with TBI highlights the fact that pediatric brain injury remains underinvestigated. Pediatric physicians are left to make deductions from guidelines developed for adult populations (3) or to call upon their clinical experience to make individual treatment decisions.

Evidence-based medicine is playing an increasing role in the direction of medical practice. As an empirical, unbiased analysis of the state of the literature on a given topic, an evidence report summarizes vast bodies of literature such that the practitioner can more confidently base therapeutic choices on a scientific foundation. By this means, one is able to understand not only the evidence supporting various therapeutic options but also the rigor of the evidence. A management decision based on solid (class I) evidence should offer the highest degree of confidence that the correct choice has been made. At the other extreme, a decision based on much less solid (e.g., class III) evidence may be equally efficacious, but it alternatively may not be the best choice, and the results of that decision should be followed closely so that alterations can be expediently made if necessary. The majority of management decisions are not and never will be supported by class I evidence. As such, knowing the degree of support for a given decision, as well as the alternatives, should be an extremely valuable adjunct to the practice of medicine.

The evidence-based "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" for adults (4) have been exceptionally well received by a large audience of physicians, paramedical personnel, and administrators around the world. Although to a lesser extent than would be optimally expected, the adult guidelines have changed practice and improved outcome from severe TBI. Notably, however, the evidentiary foundation on which they are based did not specifically address the pediatric population. One of the most common questions asked following presentations of the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" addresses

how they apply to children. The proper answer to date has been that this is unknown. Since it is not true that "children are just little adults," it is not proper to generalize from the adult literature to the pediatric population. The present effort is an attempt to address this problem by providing a companion to the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" that addresses issues from that work as they apply to children while additionally covering aspects of TBI care that are unique to or differently developed in the pediatric population. A number of the pediatric recommendations at the option level mirror those in the adult guidelines. In both the adult and pediatric guidelines, these were derived based on consensus.

These guidelines address key issues relating to the management of severe TBI in pediatric patients with a Glasgow Coma Scale score of 3–8. Pediatric is defined as <18 yrs of age. Traumatic brain injury is defined as primary or secondary injury to the brain resulting from a traumatic etiology. Abusive head injury (identified by a variety of different terms including inflicted traumatic brain injury and shaken baby syndrome, among others) is included in this category. Injuries due to mechanisms such as drowning, cerebrovascular accidents, or obstetrical complications are not addressed here.

There are a number of shortcomings of relying solely on evidence reports to direct medical decision making. A major factor is that such works can only state what the literature supports. If an issue has been only poorly or incompletely researched, little strong support for it will be gleaned from the literature even if it is a currently widely accepted therapy or one that is very strongly believed to be effective on a purely clinical basis. An example in the TBI literature is the use of

mannitol to treat intracranial hypertension. This is one of the oldest treatments, and there is generally a strong medical consensus that it is an effective and proper response to elevated intracranial pressure. Because it became "clinically established" before today's more rigorous medical environment, there is surprisingly little empirical, strong scientific literature on its use. This contrasts sharply with the literature on a much newer treatment for intracranial hypertension, hypertonic saline, for which there is a fair body of reasonably strong research. Such newer treatments, having to meet higher scientific standards, are often supported by higher classes of evidence. This leads to the commonly encountered but less than satisfactory situation where older and more established therapies will be found to have less empirical support than newer treatment modalities (e.g., mannitol vs. hypertonic saline or ventricular drainage vs. lumbar drainage). The proper manner of addressing this issue when formulating treatment recommendations remains an unsettled and difficult problem in developing treatment guidelines.

Another difficulty is that generalizing from a study is inconsistent with a rigorous evidence-based process. Even if it is recognized that a given factor is highly germane to a specific question, it cannot be addressed in the absence of data on that factor in particular. An example from the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" is the list of factors that support intracranial pressure monitoring in patients with a Glasgow Coma Scale score of ≤8 and a normal admission computed tomography scan at the level of a treatment guideline. These include the presence of two or more of the following: age >40 yrs, unilateral or bilateral motor posturing, and the presence or history of a systolic blood pressure <90 mm Hg. In no way are these believed to be the most definitive or only factors that suggest a high likelihood of intracranial hypertension in comatose patients with normal computed tomography scans—they are merely the factors that arose from the class II study upon which the management guideline was based. Such a restriction on generalization maintains the scientific rigor of the evidence-based process. It is, however, also extremely unsatisfying because it severely limits our ability to address issues that are commonly thought to be important and it may produce statements that superficially appear to be incomplete. It is hoped that such shortcomings will be corrected through future research.

Process Used in the Development of These Guidelines

The project was initiated in March 2000 during the 5th Annual Aspen Neurobehavioral Conference. Three phases of treatment for pediatric TBI were identified as priorities for guidelines development—acute medical management, rehabilitation, and school/family/community reentry. Participants at the conference who are also investigators with the Evidence-Based Practice Center (EPC) of Oregon Health & Science University (OHSU) agreed to take acute medical management as their topic. They contacted individuals who had previously worked on the topic and included additional investigators from OHSU to assemble a multidisciplinary team.

Using the 14 topics from the adult guidelines as a place to begin, we added pediatric-specific questions and arrived at a set of 18 key topics, including one that addresses a critical pathway for treatment, or a treatment algorithm. Each topic was assigned a primary and secondary author. With the assistance of the EPC's reference librarian, we conducted Medline searches from 1966 to 2001 by using a broad search strategy for each question. Blinded to each other, and using predetermined criteria, the primary and secondary authors read abstracts and identified studies for which full-text articles would be retrieved. They then read the studies and eliminated another set. They used as their general criterion the goal of obtaining the best possible evidence. If studies at the best level of randomized trials were not available, then those at the next level down were accepted. Thus, the level of evidence included for each topic in this document varies with what was available in the literature.

A baseline requirement for a study to be used for recommendations at the level of standards or guidelines was that the study be about children or contain data about children that was reported separately from data reported about adults. If we could not distinguish adult data from child data in a study, or if a study did not include children, we did not include it in this review. In the case where there was no pediatric literature for a topic or for a subset of a topic, we reviewed the adult guidelines and by consensus elected how to refer to that document in terms of recommendations for children. Thus, a number of the pediatric recommendations at the options level mirror those in the adult guidelines.

Degrees of Certainty

Regarding the degree of certainty associated with a particular recommendation, the following terminology is the most widely accepted and is used in this document.

- Standards: Accepted principles of patient management that reflect a high degree of clinical certainty
- Guidelines: A particular strategy or range of management strategies that reflect a moderate clinical certainty
- Options: The remaining strategies for patient management for which there is unclear clinical certainty

Note that "guideline" is used both in a global sense, that is, clinical practice guidelines, as well as in a more specific sense, as noted previously.

Classification of Evidence

When assessing the value of therapies or interventions, the available data are classified into one of three categories according to the following criteria:

- Class I evidence: randomized controlled trials—the gold standard of clinical trials. However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodological inadequacies.
- Class II evidence: clinical studies in which the data were collected prospectively and retrospective analyses that were based on clearly reliable data. Types of studies so classified include observational studies, cohort studies, prevalence studies, and case control studies.
- Class III evidence: most studies based on retrospectively collected data. Evidence used in this class indicates clinical series, databases or registries, case reviews, case reports, and expert opinion.

Correlation Between Evidence and Recommendations

Standards are generally based on class I evidence. However, strong class II evi-

Developmental Phase	Mortality	Developmental Category					
		Somatic		Intellectual/Cognitive		Behavioral	
		Neurological/Hormonal	Sensorimotor	Executive Function	Language	Emotional	Social
Infancy 0 – 6 months							
Infancy 7 – 12 months							
Infancy 13 – 18 months							
Infancy 19 – 24 months							
Childhood 2 years							
Childhood 3 – 4 years							
Childhood 5 – 6 years							
Childhood 7 – 8 years							
Pre-puberty 9 – 11 years							
Early Adolescence 11 – 14 years							
Late Adolescence 15 – 20 years							

Figure 1. Matrix.

dence may form the basis for a standard, especially if the issue does not lend itself to testing in a randomized format. Conversely, weak or contradictory class I evidence may not be able to support a standard.

Guidelines are usually based on class II evidence or a preponderance of class III evidence.

Options are usually based on class III evidence and are clearly much less useful except for educational purposes and in guiding future studies.

Pediatric Conceptual Model

Three dimensions constitute the conceptual model necessary to evaluate and understand outcomes from brain injury in children and adolescents and the effect of interventions on those outcomes:

- Developmental category of outcome
- Developmental phase of child at time of injury
- Injury severity

Because outcomes from brain injury are observed in cognitive and behavioral dimensions, as well as somatic dimensions, evaluation of the recovery process in children is confounded by cognitive and behavioral changes that occur as a function of normal development (2). Furthermore, development within each dimension accelerates and decelerates during different developmental phases. Injury severity, and the presence or absence of multiple-system injuries, will also interact with the child's age to influence outcome.

The matrix in Figure 1, adapted from several sources (5–7), offers a framework for considering the complexity of measuring outcomes from brain injury in children.

The horizontal axis represents the various categories within which outcomes can be observed. The vertical axis represents developmental phases that influence expected performance within developmental category. The third dimension of injury severity, not represented on this matrix, introduces more complexity to the consideration of outcome. This model applies to all of the questions addressed in these guidelines. Its utility is to map existing research for each question; empty cells indicate topics for future study.

An additional issue specific to pediatric trauma is that of intentional injury. The nature of the trauma and secondary complications are thought to be distinct in ways from many unintentional injuries, requiring corresponding differences in appropriate treatment. The delay between injury and hospital admission, or between admission and recognition that the injury was intentional, can thwart timely treatment decisions. Although at the beginning of the project we agreed to pay careful attention to this issue in our review of the literature, no studies provided data of any kind to assist in making distinctions about treatment for intentional injury.

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Chapter 2: Trauma systems, pediatric trauma centers, and the neurosurgeon

I. RECOMMENDATIONS

A. *Standards*. There are insufficient data to support a treatment standard for this topic.

B. *Guidelines*. In a metropolitan area, pediatric patients with severe traumatic brain injury (TBI) should be transported directly to a pediatric trauma center if available.

C. *Options*. Pediatric patients with severe TBI should be treated in a pediatric trauma center or in an adult trauma center with added qualifications to treat children in preference to a level I or II adult trauma center without added qualifications for pediatric treatment.

D. *Indications from Adult Guidelines*. The adult guidelines (1) recommend organized trauma systems as a guideline and the services of a neurosurgeon as an option in the treatment of brain trauma. They cite studies that demonstrate overall reduction in mortality rate after implementation of trauma systems, and they use the *Resources for Optimal Care of the Injured Patient* of the American College of Surgeons Committee on Trauma (2) as a foundation for their recommendations.

II. OVERVIEW

Although a number of studies report decreased mortality rate with implementation of trauma systems and use of pediatric trauma centers (3–6), recent research suggests that survival in certain subgroups may not be improved. Mann et al. (7) found a significant increase in deaths due to TBI from pre- to postimplementation of Oregon's trauma system for patients who were injured in rural areas and transferred to a higher level of care. For patients who died, transfer time from level 3 and level 4 rural hospitals increased after the trauma system was established. The number of patients with TBI who were transferred for neurologic examination also increased. Authors suggest that trauma system protocols for ex-

peditious transfer may have the unintended result of subjecting unstable patients to premature transfer.

Trauma systems, pediatric trauma centers, and caregivers who are specifically trained to treat children are all components of a system of care designed to provide better outcomes for patients. For this section, studies were identified that address isolated components of this system of care and present the findings. It must be emphasized that, ultimately, outcome is a function of the system and not of its isolated components.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 24 potentially relevant studies, three were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Three studies, two retrospective (4, 6) and one prospective (5), provide limited evidence of the influence of trauma systems and pediatric trauma centers on mortality rates for children who sustain moderate to severe TBI. One of the three (6) also evaluates the effect of being a pediatric trauma center on the number of neurosurgical procedures provided to patients. The number of procedures could be considered a surrogate indicator of intensity of treatment and therefore an indirect link to outcome.

Pediatric Trauma Centers

Potoka et al. (6) conducted a retrospective review of medical records of patients 0–16 yrs old treated at pediatric or adult trauma centers in the state of Pennsylvania between 1993 and 1997. Four patient groups were specified, according

to the type of trauma center in which they were treated:

- PTC: pediatric trauma center (n = 1,077)
- ATC AQ: adult trauma center with added qualifications to treat children (n = 909)
- ATC I: level I adult trauma center (n = 344)
- ATC II: level II adult trauma center (n = 726)

Whereas the study included patients with mild and moderate TBI, this evaluation is based on the patients with severe TBI (Glasgow Coma Scale score 3–8). Dependent variables were mortality rate, number of neurosurgical procedures, and mortality rate for patients who received neurosurgical procedures.

Method of and criteria for referral and transfer within the statewide system are not discussed in this publication. Distributions for injury severity based on injury severity score are presented for the parent group of all traumas but not for the subgroup of TBI.

This class III study suggests the following:

1. Pediatric patients with severe TBI are more likely to survive if treated in PTCs, or ATC AQs, than in level I or level II ATCs.

2. The pediatric patient with severe TBI who requires neurosurgical procedures has a lower chance of survival in level II ATCs vs. the other centers.

Johnson and Krishnamurthy (5) conducted a prospective, nonrandomized comparison of mortality rate among admitted patients, some of whom were transported directly to Children's Hospital in Washington, DC, a level I PTC, and some of whom were first transported to other hospitals and then transferred to Children's Hospital in Washington, DC.

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Potoka (6) 2000	Retrospective medical record review of children treated for head injury (GCS score range, 3–15; age, 0–16 yrs) at accredited trauma centers in Pennsylvania with data entered in the Pennsylvania Trauma Outcome Study registry between 1993 and 1997. Data for this review include moderate (GCS, 9–12; n = 588) and severe (GCS, 3 to 8; n = 2,468) patients, n = 3,056. GCS score is not specified. Independent variable: level of pediatric accommodation in trauma center (PTC, ATC AQ, ATC I, ATC II). Dependent variables: mortality, neurosurgical procedures, mortality for patients receiving neurosurgical procedures. Analysis: Student's t-test, Mann-Whitney U, χ^2, Fisher's exact. No use of multivariate statistics. Results were not stratified by age. Baseline differences in ages between groups are not accounted for.	III	Survival higher in PTC or ATC AQ than level I or II ATCs for severe TBI. Equal chance of survival for severe TBI requiring neurosurgery in PTC, ATC AQ, or level I ATC, but not level II ATC. Equal chance of survival for moderate TBI, regardless of facility. For moderate TBI, more likely to have neurosurgery in PTC or level I ATC, and if they do, less likely to die; less likely to have neurosurgery in ATC AQ or level II ATC, and if they do, more likely to die.
Johnson et al. (5) 1996	Prospective, nonrandomized comparison of direct (n = 135) vs. indirect (n = 90) transports to level I PTC. Children (n = 225; age, 1–12 yrs) seen by neurosurgical services at Children's Hospital in Washington, DC, between 1985 and 1988. Severity stratified by admission GCS (moderate, 9–12; severe, ≤8). Independent variable: direct vs. indirect transport. Dependent variable: mortality. Analysis: χ^2, Mann-Whitney U, Fisher's exact. No use of multivariate statistics. Baseline differences: for entire sample (including milds), LOS in PICU was significantly shorter for direct transport group; percent intubated at arrival was greater for indirect transport group; significantly greater child abuse and child abuse as cause of death in indirect transport group; for patients with GCS 3–8, trauma score was significantly higher in direct transport group (score = 9) than indirect transport group (score = 7).	II	For severe TBI, survival higher for direct transport patients than indirect transport patients. Equal chance of survival for moderate TBI, regardless of transport method.
Hulka et al. (4) 1997	Population-based (Washington and Oregon) retrospective medical record review of children <19 yrs old, hospitalized with at least one discharge diagnostic code between 800 and 959 (excluding 905–909, late effects of injury; 930–939, foreign bodies; 958–trauma complications. Severity stratified by ISS (minor, 1–15; serious, >15). Independent variable: presence or absence of trauma system. Dependent variable: mortality. Compared mortality between Oregon and Washington before (1985–1987) and after (1991–1993) Oregon implemented its statewide trauma system. All traumas/Oregon/before: 14,082 All traumas/Washington/before: 18,525 All traumas/Oregon/after: 8,981 All traumas/Washington/after: 12,991 Numbers for head injury not reported per group. Analysis: Multiple logistic regression model to calculate risk adjusted odds of death. IVs in model: trauma system, age, gender, severity, AIS scores, and multiple injuries (AIS score of 2 or more in more than one AIS region).	III	For all severity levels and all injuries, no significant difference between states in mortality before or after trauma system. For severe traumas and all injuries, no significant difference between states in mortality before trauma system; mortality significantly higher in Washington than Oregon after trauma system. Before trauma system, decreasing age, and maximum AIS head, chest, and abdomen associated with risk of death. After trauma system, maximum AIS head and abdomen remained.

GCS, Glasgow Coma Scale; PTC, pediatric trauma center; ATC, adult trauma center; AQ, with added qualifications; TBI, traumatic brain injury; LOS, length of stay; PICU, pediatric intensive care unit; IV, independent variables; AIS, Abbreviated Injury Score.

Table 2. Pediatric mortality after acute trauma in Oregon and Washington, before and after implementation of a statewide trauma system in Oregon

Interval	State	
	Oregon	Washington
1985–1987	No trauma system (n = 14,082)	No trauma system (n = 18,525)
1991–1993	Statewide trauma system (n = 8,981)	No trauma system (n = 12,991)

Patients included children 1–12 yrs of age treated in neurosurgical services between 1985 and 1988.

Severity stratification included mild (Glasgow Coma Scale score 13–15), moderate (Glasgow Coma Scale score 9–12) and severe (Glasgow Coma Scale score ≤8) TBI. Our present interest is only the

*C*hildren with severe traumatic brain injury are more likely to survive if treated in pediatric trauma centers or in adult trauma centers specially equipped and staffed to accommodate pediatric patients.

patients in this study who sustained severe brain injury: 56 who received direct transport and 42 who received indirect transport. However, statistical significance was only reported for the overall group, which included patients with mild and moderate TBI. Mortality rate for all patients was significantly greater in the indirect transport group (4.7%) than the direct transport group (1.9%).

An important baseline difference between groups was noted for severe TBI patients. The trauma score was significantly higher in the direct transport group (n = 9) than the indirect transport group (n = 7), indicating that the patients in the latter group were less stable physiologically. Authors suggest that this is better viewed as an outcome than a baseline difference and that the physiologic deterioration occurred as a function of delays in appropriate treatment due to the transfer.

This class II study suggests that in this metropolitan area, pediatric patients with severe TBI are more likely to survive if transported immediately to a PTC than if transported first to another type of center and then transferred to a PTC.

Trauma Systems

Hulka et al. (4) compared mortality rates between two states (Oregon and Washington) during two periods of time: before (1985–1987) and after (1991–1993) Oregon implemented a statewide trauma system (Table 2). This retrospective medical record review was an evaluation of all injured pediatric patients <19 yrs of age hospitalized with at least one discharge diagnostic code indicative of acute trauma. The sample sizes for subgroups of patients with TBI were not reported. Multiple logistic regression modeling was used to calculate the risk-adjusted odds of death. Independent variables were trauma system, age, gender, severity, Abbreviated Injury Severity Scores, and multiple injuries.

For all severe traumas, the risk of death was significantly higher in Washington than Oregon after Oregon implemented its trauma system. For TBI, maximum Abbreviated Injury Severity Score for head was the strongest predictor of risk of death both before and after implementation of the trauma system, with little change in the odds ratio (1.25 before and 1.29 after the trauma system). Thus, this class III study suggests no effect of the trauma system on risk of mortality from TBI.

V. SUMMARY

Children with severe TBI are more likely to survive if treated in pediatric trauma centers or in adult trauma centers specially equipped and staffed to accommodate pediatric patients. In a metropolitan area, direct transport to a PTC appears to increase survival rate overall. There has been no evaluation of functional outcome for this topic.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Large data sets have accumulated from studies evaluating trauma systems that contain sufficient sample size and variables to allow multivariate analyses focused on specific subgroups of patients. These data sets should be used to identify pediatric patients with TBI, to stratify by age and injury severity, and to evaluate outcome based on differences in care such as trauma systems and PTCs. Unfortunately, outcome measures in existing studies are limited to mortality or very short-term morbidity. Prospective studies that link acute medical management with long-term outcome are needed to understand the effect of systems of care on children with TBI.

Novel methodological technology for evaluating systems from the discipline of systems science could be directly applied to questions about medical systems of care to provide a better understanding of both the intended and unintended results of implementation of new systems.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 2. Trauma Systems, Pediatric Trauma Centers, and the Neurosurgeon

1. trauma centers/
2. trauma systems.tw.
3. 1 or 2
4. exp craniocerebral trauma/
5. head injur$.tw.
6. brain injur$.tw.
7. 4 or 5 or 6
8. 3 and 7
9. limit 8 to human
10. limit 9 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 3. Prehospital airway management

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support treatment standards for this topic.

B. Guidelines. Hypoxia must be avoided if possible and attempts made to correct it immediately. Supplemental oxygen should be administered.

There is no evidence to support an advantage of endotracheal intubation (ETI) over bag-valve-mask (BVM) ventilation for the prehospital management of the airway in pediatric patients with traumatic brain injury (TBI).

C. Options. If prehospital ETI is instituted for pediatric TBI patients, then specialized training and use of end-tidal CO_2 detectors is necessary.

D. Indications from Adult Guidelines. Under *Guidelines* (1), the authors state "hypoxemia must be avoided, if possible, or corrected immediately. . . .Hypoxemia should be corrected by administering supplemental oxygen." Under *Options*, the authors state that the "airway should be secured in patients who have severe head injury (GCS <9), the inability to maintain an adequate airway, or hypoxemia not corrected by supplemental oxygen. Endotracheal intubation, if available, is the most effective procedure to maintain the airway."

II. OVERVIEW

Large prospective randomized studies in the prehospital setting addressing the effects of hypoxia, abnormal ventilation, and inadequate airway and possible benefits of invasive airway management have not been conducted in either adult or pediatric populations. A large prospective observational cohort study using the Traumatic Coma Data Bank that included some prehospital information showed that hypoxemia in the prehospital setting was associated with worse outcomes in TBI patients (2).

Several studies suggest that hypoxia during prehospital care of children with severe TBI is common. A small study of 25 consecutive pediatric trauma patients showed that 16% had pulse oximetry readings <75% and an additional 28% had a readings of 75–90% during prehospital care (3). Another study also demonstrated the high frequency of hypoxemia in prehospital TBI patients. Of 131 patients who were retrospectively reviewed, 27% were hypoxic on arrival to the emergency department (4). A retrospective chart review of 72 pediatric patients admitted to a single level I pediatric trauma center with a postresuscitation Glasgow Coma Scale (GCS) score of 6–8 demonstrated that 13% had a documented hypoxemic episode somewhere during the continuum of care from the prehospital setting to the intensive care unit. However, the presence of hypoxia was not statistically related to outcome in this relatively small study (5).

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 35 potentially relevant studies, four were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Few studies have been conducted in the prehospital airway management of pediatric patients and only one that specifically evaluated the role of intubation in severe pediatric TBI patients. The only prospective class II study involved a randomized controlled trial of the airway management of all pediatric patients seen in two large urban emergency medical systems. A total of 830 patients ≤12 yrs of age were randomized to airway management by BVM vs. ETI on an odd-even day allocation with a total of 23 (2.8%) protocol violations. No pharmacologic adjuncts were used, and end-tidal CO_2 monitoring was documented in 77% of intubated patients. Of the 420 patients assigned to ETI, 115 (27%) only received BVM; 177 of the remaining 305 were successfully intubated (success rate 73%), and three had unrecognized esophageal intubations. Overall, no benefit was found in ETI in this study or in any of the prospectively derived patient subgroups. Among children with severe TBI, the subgroup analysis, using a strict intention-to-treat analysis, showed that eight of 25 in the BVM group vs. nine of 36 in the ETI group survived (odds ratio, 0.71; 95% confidence interval, 0.23–2.19), and two of 25 in the BVM vs. four of 36 in the ETI group had a "good neurologic outcome" (odds ratio, 1.44; 95% confidence interval, 0.24–8.52). Although this was the largest prospective prehospital study to date, there is significant risk of a type I error in the subgroup analysis for TBI patients alone (6).

A large retrospective study that used the National Pediatric Trauma Registry phase 3 abstracted all records of patients with Abbreviated Injury Severity score ≥4 if they received either BVM or ETI by prehospital providers. A total of 578 case records met this eligibility out of the total registry population of 31,464. Endotracheal intubation was used in 479 (83%) and BVM in 99 (17%). The two cohorts did not differ in injury severity or mechanism but did differ in age stratification (ETI group older), the use of intravenous fluids (81% of ETI, 71% of BVM, $p < .05$), the use of intravenous medications (39% of ETI vs. 23% of BVM, $p < .05$), and transport by helicopter (67% of ETI vs. 27% of BVM, $p < .01$). Forty-eight percent of each cohort died. Injury complications of any organ system were less frequent in the ETI group (58%) vs. BVM group (71%, $p < .05$). Functional outcome using the Functional Independence Measure in patients >7 yrs old showed a nonsignificant trend in improved outcome in the ETI patients.

Another smaller retrospective study at a single tertiary referral level I pediatric trauma center during 1987 evaluated ETI in patients in the field, at the referring facility, or in the institution's own emer-

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Nakayama et al. (7), 1990	Trauma registry of all hospitalized patients at one tertiary pediatric center over 1 yr who underwent ETI of which 14 of 605 total were prehospital attempts.	II	Only 8/16 successful with two cricothyroidotomy attempts (1/2 successful), whereas 36/36 (p <.0002) at referring hospital and 17/17 (p <.001) at tertiary hospital were successful. Insufficient numbers to stratify by severity.
Gausche et al. (6), 2000	RCT of prehospital airway management alternating BVM vs. ETI by odd/even days over 3 yrs. Total 820 eligible patients, of which 61 were TBI alone.	II	Using intention-to-treat analysis, 8/25 BVM vs. 9/36 ETI survived (OR, 0.71; 95% CI, 0.23–2.19) and 2/25 BVM vs. 4/36 ETI had "good" neurologic outcome (OR 1.44, 95% CI 0.24–8.52).
Murray et al. (10), 2000	Retrospective registry-based review of all severe TBI patients (age ≥11 yrs, GCS ≤8 with head AIS ≥3) admitted to a single combined adult and pediatric level I trauma center over 3-yr period.	II	For patients 11–20 yrs non-risk-adjusted MR of prehospital intubated patients 19/22 vs. nonintubated 57/115 (MR, 1.74; 95% CI, 1.36–2.23; p = .001) and unsuccessful prehospital intubation 7/10 vs. nonintubated 57/115 (MR, 1.41; 95% CI, 0.90–2.21; p = .325). Risk adjustment only done for entire cohort. No survival benefit to attempted prehospital intubation in severe TBI patients.
Cooper et al. (11), 2001	Retrospective analysis of 31,464 records of NPTR-3 for severe TBI (head AIS ≥4,578 patients) stratified by field airway management ETI (479/578) vs. BVM (99/578).	II	Similar injury severity and mechanism, ETI group older, more often received intravenous fluids and medications, and more often transported by helicopter. MR 48% both groups; FIM <6 in ETI group 65.7% vs. BVM 65.2%, p = NS; ETI less complications (58%) vs. BVM (71%), p <.05.

ETI, endotracheal intubation; RCT, randomized controlled trial; BVM = bag-valve-mask intubation; TBI, traumatic brain injury; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Severity; MR = mortality ratio; NPTR-3, National Pediatric Trauma Registry phase 3; FIM, Functional Independence Measure; NS, nonsignificant.

gency department. The authors reported a success rate of only nine of 16 in the field (including one successful and one unsuccessful cricothyrotomy) compared with 36 of 36 at the referring facility (p < .0002) and 17 of 17 in a level I emergency department (p < .001). The authors attributed four deaths in patients who received prehospital ETI to "major airway mishaps." The small numbers did not allow adjustment for injury severity (7).

Another registry-based retrospective cohort study that used patients admitted to the 13 trauma centers in Los Angeles County from 1995 to 1997 evaluated prehospital ETI in patients with a GCS ≤8 and a head Abbreviated Injury Severity score ≥3. There were a total of 137 patients aged 11–20 yrs old (ETI was not allowed in younger patients), among whom 22 were successfully intubated. Mortality rate was 19 of 22 in successful ETI group vs. 57 of 115 in BVM group (unadjusted mortality rate, 1.74; 95% confidence interval, 1.36–2.23; p < .001), and mortality rate was seven of ten in unsuccessful intubation vs. 57 of 115 in the BVM group (unadjusted mortality rate, 1.41; 95% confidence interval, 0.90–2.21; p = .325). There was no risk stratification within this pediatric age cohort in the study.

Key Elements From the Adult Guidelines Relevant to Pediatric TBI

Several studies have documented that adult patients with severe TBI who develop hypoxia have decreased risk of survival. A large prospective observational study of 717 patients with severe TBI admitted to four level I acute trauma centers that participated in the Traumatic Coma Data Bank reported that an episode of hypoxia (Pa_{O_2} ≤60 mm Hg or apnea or cyanosis in the field) was independently associated with a significant increase in morbidity and mortality rates from severe head injury (2).

Another large retrospective cohort study of patients with severe TBI (GCS <9 and head or neck Abbreviated Injury Severity score >4) involved a total of 1,092 TBI patients of whom 351 had isolated TBI. The investigators found that 26% of patients intubated in the prehospital setting died compared with 36.2% of nonintubated patients (p < .05), and in the subgroup analysis of isolated TBI patients, 22.8% of patients who were intubated before admission to a hospital died compared with 49.6% of nonintubated patients (p < 0.05) (8).

A study of 50 consecutive TBI patients who were transported by an aero-medical service and were intubated (median GCS 7, SD 2, age 5–84 yrs) were prospectively evaluated by pulse oximetry. Among patients with a pulse oximetry reading >90%, 14.3% (three of 21) died and 4.8% had severe disability, whereas 27.3% (six of 22) of patients with a pulse oximetry of 60–90% died and 27.3% (six of 22) had severe disability. Finally, among patients with pulse oximetry <60%, the mortality rate was 50% (three of six) and severe disability rate was 50% (three of six, p = .005). This study reports a strong association of preintubation hypoxemia with poor neurologic outcome in severe TBI patients, but there was no evaluation of different methods for airway management. The outcomes of pediatric patients were not reported separately (9–11).

V. SUMMARY

There are no well-conducted, prospective outcome studies with sufficient power to evaluate the role of various airway maneuvers in pediatric prehospital TBI care. On one hand, there is clear evidence that hypoxemia leads to poorer neurologic outcome in both pediatric and adult TBI patients. There is ample evidence also that hypoxemia frequently occurs in the prehospital setting in this

> *S*hort of this type of study, clinicians will need to infer from smaller studies whether there is a role for prehospital intubation in pediatric patients with traumatic brain injury.

patient population. On the other hand, there is evidence that successful prehospital intubation of infants and children requires specialized training, and reported success rates are generally less than in adults. Furthermore, there is much less evidence that aggressive prehospital airway management changes outcome for either adults or children. In the largest prospective airway study (adult or pediatric) yet, there was no benefit overall or to any subgroup analyzed (including TBI) attributed to endotracheal intubation by paramedics in pediatric patients (6).

VI. KEY ISSUES FOR FUTURE INVESTIGATION

As with most areas of clinical medicine, large randomized, controlled trials are lacking that would clearly define suitable interventions including prehospital airway management for the pediatric TBI patient. Given that the largest prehospital randomized, controlled trial study to date of pediatric emergency airway management included very few children with TBI, it is difficult to conceive that an even larger study of TBI patients will be accomplished soon.

Short of this type of study, clinicians will need to infer from smaller studies whether there is a role for prehospital intubation in pediatric TBI patients. The potential benefits of intubation in preventing and treating hypoxemia vs. the known risks (unrecognized esophageal or mainstem bronchus intubation) will need to be carefully balanced.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 3. Prehospital Airway Management

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. limit 4 to (human and English language and "all child <0 to 18 years>"
6. vascular access.mp.
7. bone marrow.mp.
8. intraosseous.mp.
9. exp intubation, intratracheal/ or "intratracheal intubation".mp.
10. exp Airway obstruction/th [Therapy]
11. "AIRWAY MANAGEMENT".mp.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12

Chapter 4. Resuscitation of blood pressure and oxygenation and prehospital brain-specific therapies for the severe pediatric traumatic brain injury patient

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. Hypotension should be identified and corrected as rapidly as possible with fluid resuscitation. In children, hypotension is defined as systolic blood pressure below the fifth percentile for age or by clinical signs of shock. Tables depicting normal values for pediatric blood pressure by age are available (1). The lower limit of systolic blood pressure (5th percentile) for age may be estimated by the formula: 70 mm Hg + (2 × age in years) (2). Evaluation for associated extracranial injuries is indicated in the setting of hypotension.

C. Options. Airway control should be obtained in children with a Glasgow Coma Score ≤8 to avoid hypoxemia, hypercarbia, and aspiration. Initial therapy with 100% oxygen is appropriate in the resuscitation phase of care. Oxygenation and ventilation should be assessed continuously by pulse oximetry and end-tidal CO_2 monitoring, respectively, or by serial blood gas measurements.

Hypoxia (defined as apnea, cyanosis, Pao_2 <60–65 mm Hg, or oxygen saturation <90%) should be identified and corrected rapidly. Hypoventilation (defined as ineffective respiratory rate for age, shallow or irregular respirations, frequent periods of apnea, or measured hypercarbia) is also an indication for airway control and assisted ventilation with 100% oxygen in the resuscitation phase of care.

Blood pressure should be monitored frequently and accurately. Timely fluid administration should be provided to maintain systolic blood pressure in the normal range. Charts with normal values based on age are available (1). Median (50th percentile) systolic blood pressure for children older than 1 yr may be estimated by the formula: 90 + (2 × age in years) (2).

Sedation, analgesia, and neuromuscular blockade can be useful to optimize transport of the patient with traumatic brain injury (TBI). The choice of agents and timing of administration are best left to local Emergency Medical Services protocols.

The prophylactic administration of mannitol is not recommended. Mannitol may be considered for use in euvolemic patients who show signs of cerebral herniation or acute neurologic deterioration.

Mild prophylactic hyperventilation is not recommended. Hyperventilation may be considered in patients who show signs of cerebral herniation or acute neurologic deterioration, after correcting hypotension or hypoxemia.

D. Indications from the Adult Guidelines. In the adult guidelines for the prehospital management of severe TBI (3, 4), specific age-dependent ventilatory rates were provided as shown in Table 1.

II. OVERVIEW

In TBI literature on both children and adults, there is a growing understanding of the extreme sensitivity of the injured brain to secondary insults, both systemic and intracranial (3, 5–15). Secondary systemic insults are common in pediatric severe TBI. The systemic secondary insults that appear to have the most impact on outcome are hypoxia and hypotension.

The adult neurosurgical literature has traditionally defined hypotension as systolic blood pressure <90 mm Hg. In children, hypotension can be defined as less than the 5th percentile of normal systolic blood pressure for age. However, it should be emphasized that hypotension is a late sign of shock in children. Pediatric patients may maintain their blood pressure despite significant hypovolemia and clinical signs of shock. Signs of decreased perfusion include tachycardia, loss of central pulses, decreased urine output below 1 mL·kg^{-1}·hr^{-1}, or increased capillary filling time of >2 secs.

In children, fluid resuscitation is indicated for clinical signs of decreased perfusion even when an adequate blood pressure reading is obtained. Shock is almost never due to head injury alone; evaluation for internal or spinal cord injury is indicated (16). Fluid restriction to avoid exacerbating cerebral edema is contraindicated in the management of the head-injured child in shock (17). If peripheral vascular access is difficult in children, intraosseous infusion of fluids and medications is indicated (18).

Apnea and hypoventilation are common in pediatric severe TBI. As in adults, hypoxia may be defined by Pao_2 <60–65 torr or oxygen saturation <90%. However, hypoxia develops more rapidly in the child than in the adult during apnea or hypoventilation (19). Central cyanosis is neither an early nor a reliable indicator of hypoxemia in children. Also, adequate oxygenation does not necessarily reflect adequate ventilation. Respiratory rate and effort should be monitored and corrected to age-appropriate parameters.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 133 potentially relevant studies, eight were used as evidence for this question (Table 2).

IV. SCIENTIFIC FOUNDATION

The negative impact of hypoxia and hypotension on the outcome of severe

Table 1. Age-dependent ventilatory rates (breaths/min) for eucapnea and hyperventilation

Age	Rate for Eucapnea	Rate for Hyperventilation
Adults	10	20
Children	20	30
Infants	25	35

TBI has been demonstrated repeatedly in studies of mixed adult and pediatric populations (3, 6, 7, 12–14). In these studies, hypoxia, hypercarbia, and hypotension were common and correlated with increased morbidity and mortality rates.

Hypoxia

Pigula et al. (10) analyzed the influence of hypoxia and hypotension on mortality from severe TBI (Glasgow Coma Scale ≤ 8) in two prospectively collected pediatric (age ≤ 16 yrs) databases. Hypoxia was defined as an emergency department admission PaO_2 ≤ 60 mm Hg. For both the single-center database (n = 58) and the multiple-center database (n = 509, including the 58 from the single center), the presence of hypoxia alone did not significantly alter mortality rate. The combination of hypotension and hypoxia only slightly (and not significantly) increased the mortality rate over hypotension alone. It was concluded that hypotension is the most influential secondary insult determining short-term mortality rate. Hypotension with or without hypoxia was associated with mortality rates approaching those found in adults. Neither the degree nor the duration of hypoxia was quantified. The participating centers were well-developed pediatric trauma centers. As such, the apparent diminution in the effect of hypoxia on outcome might partially reflect the increased availability of effective airway management protocols for the prehospital situation.

Michaud et al. (20) found that level of oxygenation was associated with both mortality rate and the severity of disability of survivors. Concurrent chest injuries were strongly associated with increased mortality and morbidity rates. Children with PaO_2 levels between 105 and 350 mm Hg had significantly worse outcomes than those with PaO_2 >350 mm Hg.

In a prospective study of 200 children, Mayer and Walker (21) found that mortality rate was 55% in the presence of hypoxia, hypercarbia, or hypotension and only 7.7% without any of these factors present ($p < .01$). In a prospective cohort study by Ong et al. (22) in Kuala Lumpur, the presence of hypoxia increased the probability of a poor outcome by two- to four-fold. In the setting of abusive head trauma, Johnson et al. (23) found that apnea was present in the majority of patients and 50% were also hypotensive. It was concluded that cerebral hypoxia and/or ischemia was more strongly associated with poor outcome than mechanism of injury.

Resuscitation of Blood Pressure

Five studies directly addressed the influence of early hypotension on outcome from TBI. The impact of hypertension on survival was also addressed in two studies.

In the aforementioned study by Pigula et al. (10), they reported an 18% incidence of hypotension (defined as either a systolic blood pressure ≤ 90 mm Hg or a systolic blood pressure $\leq$ 5th percentile for age) on arrival to the emergency department. A mortality rate of 61% was associated with hypotension on admission vs. 22% among patients without hypotension. When hypotension was combined with hypoxia, the mortality rate was 85%. Hypotension was a statistically significant predictor of outcome with a positive predictive value of 61%. Early hypotension negated the improvement in survival from severe TBI that is generally afforded by youth.

Kokoska et al. (24) performed a retrospective chart review of all pediatric patients admitted to a single level 1 trauma center over a 5-yr period. They limited their patient populations to children with nonpenetrating TBI with postresuscitation age-adjusted Glasgow Coma Scale scores between 6 and 8 (n = 72). They indexed secondary insults occurring during transport to the emergency department up through the first 24 hrs in the intensive care unit. Hypotension was defined as ≥ 5 min at or below the 5th percentile for age according to the Task Force on Blood Pressure Control in Children (1). The majority of hypotensive episodes occurred during resuscitation in the emergency department (39%) and the pediatric intensive care unit (37%). Patients left with moderate and severe disability had significantly more hypotensive episodes than those with good outcomes.

Michaud et al. (20) found that hypotension in the field and emergency department was significantly related to mortality rate in children. In a data bank study from four centers, Levin et al. (25) found that outcome was poorest in patients 0–4 yrs old, which was the group that demonstrated high rates of hypotension (32%).

In a prospective series of 6,908 adults and 1,906 children <15 yrs of age at 41 centers, Luerssen et al. (26) found that hypotension was significantly associated with higher mortality rates in children. They reported a greater deleterious effect of hypotension in children than adults. Notably, children with severe hypertension had the lowest mortality rate.

In a recent retrospective study, White et al. (27) found that odds of survival in severe pediatric TBI increased 19-fold with maximum systolic blood pressure >135 mm Hg, also suggesting that supranormal blood pressures are associated with improved outcome. In contrast, previous retrospective studies (28, 29) correlated early arterial hypertension with a worse neurologic outcome.

Brain Injury Specific Treatments in Prehospital Management

There is no evidence specifically dealing with the efficacy of any of the key brain-directed prehospital therapies, including sedation and neuromuscular blockade, mannitol, hypertonic saline, or hyperventilation on the outcome from severe pediatric TBI. The scientific foundation for the in-hospital use of these agents is discussed in separate sections of this document. Extrapolation of their use to the prehospital setting may be appropriate and is provided by consensus at the level of options in the recommendations section.

Key Elements From the Adult Guidelines Relevant to Pediatric TBI

The evidence-based review of the literature on prehospital airway, breathing, and ventilation management in the adult TBI population published as the *Guidelines for Pre-Hospital Management of Traumatic Brain Injury* (4) produced two class II studies (6, 7) demonstrating that prehospital hypoxia has a statistically significant negative impact on outcome. These studies led to the following recommendation, "Hypoxemia (apnea, cyanosis,

Table 2. Evidence table

Reference	Description of Study	Data Class	Conclusion
Johnson et al. (23), 1995	Retrospective medical record and imaging review of 28 children with confirmed child abuse with significant head injury (75% male, 50% age <3 mos, stratified GCS). Those with GCS 3–8 included five shaken, seven impact injuries. Presence of fracture, GCS, SAH, SDH, contusion, DBS, IVH, apnea, intubation, early seizure, retinal hemorrhage, and outcome were noted. Analysis: Two-way tables with Fisher's exact test for categorical and Cochran-Mantel-Haenszel test for ordinal. Significance at $p < .05$.	III	No patient with clinical evidence of cerebral hypoxia and/or ischemia had a good outcome. Trauma-induced apnea causes cerebral hypoxia, which is more fundamental to outcome than mechanism of injury.
Kokoska et al. (24), 1998	Retrospective chart review, 1990–95 level I, single center, 72 children (3 mos–14 yrs 6 mos) GCS 6–8. Measures: age, gender, mechanism, injury type, duration ventilation and length of stay. Presence of hypoxia, hypotension, or hypercarbia during transport, ED, OR, and first 24 hrs in PICU. Analysis: ANOVA on continuous data. χ^2 or Fisher's exact test for nominal data. $p < .05$ was significant. Ages: 0–4 yrs, 5–9 yrs, and >10 yrs Transport time in 15-min intervals.	III	97% survival. Early hypotension linked to prolonged length of stay and worse 3-month GOS.
Levin et al. (25), 1992	Prospective databank cohort study of 103 children (<16 yrs) with severe TBI (GCS <9) at four centers. Patients received CT scan and ICP monitoring "treatment protocol." Hypotension was defined as below the age-dependent lower limit of normal systolic blood pressure. Measures: age, race, gender, mechanism, time to center, worst GCS, median ICP, pupillary reactivity, hypoxia, shock, mass lesion, skull fracture, GOS at 6 mos (86%) and 1 yr (73%). Analysis: mean/SD, box plots, logistic and linear regression.	III	Outcome was poorest in 0–4 yrs age group, which had an increased incidence of evacuated subdural hematomas (20%) and hypotension (32%). 14–21% in all age ranges were hypoxic.
Luerssen et al. (26), 1988	Prospective series of 8,814 adult and pediatric TBI patients admitted to 41 metropolitan hospitals in NY, TX, and CA in 1980–81. 21.6% pediatric TBI patients (1,906 <15 yrs) compared with adult TBI patients (6,908 >15 yrs). Measures: age, gender, admission vital signs, injury mechanism, GCS post resuscitation, pupillary response, associated injury/AIS, "major symptoms," brain injury by imaging or at surgery, and mortality rate before hospital discharge. Hypoxia not studied. Profound hypotension: systolic BP 30 mm Hg below median for age. Analysis: Two-by-two tables by Pearson's χ^2 test with Yates correction. Ordered contingency tables by Mantel-Haentzel. Logistic regression for age vs. survival.	II	Only hypotension was associated with higher mortality rate in children. Children with severe hypertension had the lowest mortality rate. Both hypotension and hypertension were associated with higher adult mortality rate. Pediatric mortality rate was significantly lower than adult mortality rate, with notable exceptions of children with profound hypotension (33.3% <15 yrs vs. 11.8% >15 yrs) or subdural hematoma (40.5% <15 yrs vs. 43.9% >15 yrs). Age, even within the pediatric age group, is a major independent factor affecting TBI mortality.
Mayer and Walker (21), 1985	Prospective study (1978–1981) of 200 consecutive children (3 wks–16 yrs, mean 5.6 yrs) with severe TBI (GCS <8). 124 male 76 female 43% IHI 57% HI/Mt Measures: age, GCS, mass lesions, oculovestibular reflexes, pupils, ICP, apnea, hypotension, hypoxia (Po_2 <60), hypercarbic (>35 torr), multiple trauma, MISS score. Interventions: ICP monitor for GCS <6, GCS 6, 7, and abnormal CT. ICP >20 (79%) received hyperventilation (Pco_2 25–28 torr), diuretic, and barbiturate protocol. Analysis: χ^2.	III	Mortality rate 21.5% IHI 10.5% HI+MT 30% 33% fixed dilated pupils 29% hypotension, hypercarbia, or hypoxia 28% altered OVR 26% mass lesions Mortality rate 55% with any hypotension, hypercarbia, or hypoxia vs. 7.7% without. 88% of HI+MT group had hypotension, hypercarbia, or hypoxia. GCS <4, increased ICP, MISS <25, hypotension, hypoxia, hypercarbia significant ($p < .01$) for poor outcome.
Michaud et al. (20), 1992	Retrospective study of prospectively collected Trauma Registry data in 75 children presenting to Harborview Medical Center with severe TBI (GCS ≤8) between January 1, 1985, and December 31, 1986. Mean 8.2 yrs; 67% male; 16% <2 yrs; 65% 3–14 yrs; 19% >14 yrs. Assessed fatality rate in system with advanced EMS and regional trauma center (83% received EMS field care). Identified factors predictive of survival and/or disability. GOS at discharge from acute care hospital measured. EMS, ED, hospital, autopsy records analyzed. Analysis: SPSS; logistic regression with EGRET; χ^2 or Fisher's exact test statistical significance; $p ≤ .05$.	II	33% fatality rate 60% associated injuries 86% intentional injuries fatal Mortality rate increased if hypotension or abnormal pupils noted in the field. ISS and pupillary reactivity predicted survival; 72-hr motor GCS and ED Po_2 predicted disability. ED Po_2 > 350 better outcome; Po_2 105–350 same outcome as hypoxic group.

Table 2. (Continued)

Reference	Description of Study	Data Class	Conclusion
Ong et al. (22), 1996	Prospective cohort study of 151 consecutive children (<15 yrs) admitted within 24 hrs of head injury (GCS <15) from 1993 to 1994 in Kuala Lumpur. Age groups: 0–4 yrs (n = 51); 5–9 yrs (n = 55); 10–14 yrs (n = 45). Stratified GCS 3–5; 6–8 Measured; age, gender, GCS admit and 24-hr, pupils, motor response, deficits, major extracranial injury, mass lesion, skull fracture, hypotension, and hypoxia. Follow-up GOS at discharge and 6 mos. Analysis: χ^2 for categorical variables. Student's t-test for continuous variables, association clinical/radiological factors, and outcome. Logistic regression for combination of factors to predict poor outcome.	II	Poor outcome related to GCS <8, abnormal pupils, motor deficits, hypoxia, hypotension, and extracranial injury. Hypoxia increases poor outcome by two- to four-fold in severe TBI. Five independent factors predict poor outcome: GCS at 24 hrs hypoxia on admission SAH DAI brain swelling on CT
Pigula et al. (10), 1993	Five-yr prospective cohort study of 58 children (<17 yrs) and a matched set of 112 adults with severe TBI (GCS <8). Group I—normal BP and PaO$_2$. Group II—hypotension or hypoxia or both. Adults compared to this subgroup. ABG, BP, GCS, ISS, PaO$_2$, age on admission, and survival were measured. Analysis: Outcome by two-tailed χ^2, Fisher's exact test, and ANOVA with Bonferroni's adjusted t-test. Statistical significance $p \leq .05$.	II	Hypotension with or without hypoxia causes significant mortality rate in children compared with levels found in adults ($p = .9$). Adequate resuscitation probably the single most critical factor for optimal survival. Survival increased four-fold with neither hypoxia nor hypotension compared with either hypoxia or hypotension ($p <.001$). When added cohort to NPTR/509 children: Hypotension increased mortality rate even without hypoxia ($p <.00001$). If both hypoxia and hypotension present, only slightly increased mortality rate than with hypotension alone ($p = .056$).

GCS, Glasgow Coma Scale; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; DBS, diffuse brain swelling; IVH, intraventricular hemorrhage; ED, emergency department; OR, operating room; PICU, pediatric intensive care unit; ANOVA, analysis of variance; GOS, Glasgow Outcome Scale; TBI, traumatic brain injury; CT, computed tomography; ICP, intracranial pressure; AIS, Abbreviated Injury Severity; BP, blood pressure; IHI, isolated head injury; HI, head injury; MT, multiple trauma; MISS, Modified Injury Severity Scale; OVR, oculovestibular reflexes; ISS, Injury Severity Score; EMS, emergency medical service; DAI, difuse axonal injury; ABG, arterial blood gas; NPTR, National Pediatric Trauma Registry.

or arterial hemoglobin oxygen saturation [SaO$_2$] ≤90 mm Hg) must be avoided, if possible, or corrected immediately. When available, oxygen saturation should be monitored on all patients with severe TBI as frequently as possible or continuously. Hypoxemia should be corrected by administering supplemental oxygen." Issues specifically pertaining to the management of airway are addressed in Chapter 3.

The "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (3) and the *Guidelines for Pre-Hospital Management of Traumatic Brain Injury* (4) produced class II (6, 7, 27, 30, 31) and class III (32–37) evidence from the adult literature that early hypotension is a statistically significant and independent factor associated with worsening outcome from TBI. From the evidence report on prediction of outcome from TBI (38), hypotension was one of the five factors found to have a ≥70% positive predictive value for mortality. Despite the solid evidence of the negative influence of early hypotension on outcome from TBI, there is much less evidence that reducing or

preventing such secondary insults improves outcome.

Regarding the use of brain-specific therapies in the prehospital setting, the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (3) and the *Guidelines for Pre-Hospital Management of Traumatic Brain Injury* (4) collectively addressed the use of sedation, neuromuscular blockade, mannitol, and hyperventilation in managing severe TBI during the prehospital period. With respect to sedation and neuromuscular blockade, they found no studies dealing directly with the effects of prehospital use of these agents on outcome from severe TBI. It was recommended at the option level that "sedation, analgesia, and neuromuscular blockade can be useful to optimize transport of the head-injured patient. Because no outcome studies provide guidance on the use of these adjuncts, the timing and choice of agents are best left to local Emergency Medical Services (EMS) protocols." (4)

The adult guidelines suggested no support for the prehospital use of mannitol. However, in two studies deleteri-

ous effects were not reported. An equally acceptable alternative position would be that mannitol is an effective but potentially hazardous method of lowering intracranial pressure and that its use during the prehospital period should be specifically limited to the euvolemic patient with evidence of cerebral herniation (a definite decrease in the level of consciousness, motor posturing or flaccidity, or pupillary changes such as anisocoria or bilateral pupillary dilation). Prophylactic use cannot be supported.

The *Guidelines for Pre-Hospital Management of Traumatic Brain Injury* (4) found no studies of the effect on outcome of the use of hyperventilation during the prehospital period. Recommendations, based on adult studies of the influence of hyperventilation used during the in-hospital period on physiologic indexes and outcome, stated; "hyperventilation (20 bpm in an adult, 25 bpm in a child, and 30 bpm in an infant) is the first line of intervention in the patient with suspected cerebral herniation." (4) Prophylactic hyperventilation was not supported.

V. SUMMARY

The literature on the influence of hypoxia and hypotension on outcome from severe TBI in adults is fairly clear. Hypotension and hypoxia are serious, and potentially preventable, secondary insults that significantly increase the morbidity and mortality rates of TBI.

Unfortunately, there is minimal specific evidence to indicate that prehospital protocols effective in preventing or minimizing hypoxic and hypotensive insults improve outcome. Therefore, despite the use of multivariate statistics to attempt to control for such confounding, the possibility remains that some, most, or all secondary insults occurring during the prehospital period that are associated with poor recovery are simply manifestations of the severity of injury and are not treatable entities.

A similar argument may be made for the pediatric literature on hypotension. Decreases in systolic blood pressure below some threshold (*vide supra*) appear to be quantitatively associated with worsening of recovery. As such, despite the absence of treatment efficacy data, maximizing efforts directed at rapid and complete volume resuscitation, coupled with protocols to minimize volume loss, are most consistent with the present body of literature and should be strongly emphasized components of prehospital care.

The situation with respect to prehospital hypoxia in pediatrics is less clear. In contrast to the adult literature, the only study that looked at prehospital hypoxia in any detail found that the presence of hypoxia alone did not significantly alter mortality rate. Such a finding, if not simply an artifact, could reflect either an increased resistance of the pediatric population to hypoxic insults in the face of severe TBI or, alternatively, unquantified efficiency of the prehospital care providers in preventing or minimizing hypoxic insults in the setting of these studies. In general, it is believed that the pediatric brain recovers better than an adult brain from a given traumatic insult. Pigula et al. (10), however, stated that they believed the occurrence of a hypotensive episode eliminated the improvement in survival from severe TBI that is generally afforded by youth. If an improved resistance to hypoxia is responsible for the lack of a demonstrated adverse influence on outcome, it is unlikely that such resistance is absolute. Therefore, although it is not proper to suggest altering treatment in the absence of specific data, it is certainly reasonable to recommend that the hypoxia avoidance/airway protection protocols afforded the patients studied by Pigula et al. (10) be set as a favorable example. Although these protocols were not specified, they did use a population from a pediatric trauma registry as a large part of their study cohort. Since such patients were treated by pediatric trauma centers, this population sample cannot be assumed to represent routine pediatric prehospital trauma care. As such, the article by Pigula et al. (10) would seem strong, albeit indirect, support for basic life support/advanced trauma life support and pediatric advanced life support protocols to be universally applied as a minimum.

There is no contributing scientific literature on the role of the prehospital administration of brain-specific therapies in improving outcome from pediatric TBI. For the same period in adults, there is no literature on neuromuscular blockade or hyperventilation, one study on a single sedative agent with very limited applicability to TBI, and two studies that indirectly address the prehospital administration of mannitol. As such, the *Guidelines for Pre-Hospital Management of Traumatic Brain Injury* base their recommendations on data from the in-hospital period and consensus opinion. In the absence of evidence that their recommendations should be specifically altered for the pediatric population, we have suggested that the adult guidelines be considered as the first line of approach. The one area where we differ in our approach is that of mannitol; the adult guidelines dispute its use, whereas we conclude that the absence of evidence for or against this agent is more consistent with the stance that mannitol is an effective but potentially hazardous method of lowering intracranial pressure and that its use during the prehospital period should be specifically limited to the euvolemic patient with evidence of cerebral herniation. Prophylactic use cannot be supported.

The presence of hypoxia or hypotension after severe TBI in children increases morbidity and mortality rates. Specific threshold values for ideal levels of oxygenation and blood pressure support in the pediatric age group have not been clearly defined. Guidelines are warranted to support avoidance or rapid correction of systolic blood pressure less than the second standard deviation of normal for

> *Resuscitation and stabilization of the cardiovascular and respiratory systems in the field, during transfer, and in the hospital need to be emphasized in an effort to optimize outcome from severe pediatric brain injury.*

age or of clinical signs of shock, apnea or hypoventilation, cyanosis, oxygen saturation <90%, or PaO_2 <60 mm Hg in children with severe head injury.

Early control of the airway and recognition and treatment of associated extracranial injuries are indicated. Despite endotracheal intubation, head-injured children remain at high risk for hypoxemia, hypercarbia, and major airway complications (39). The frequency of complications in airway procedures supports the use of protocols including medications for cerebral protection, anesthesia, pain control, and paralysis (40).

The "golden hour" clearly begins at the time of trauma. Although it is recognized that the field care of any trauma patient is encumbered both by the nature of the injury as well as by the often unfavorable and sometimes hostile environment in which it is encountered, it is apparent that whatever function is compromised by secondary insults during that period is generally not amenable to full recovery. It is therefore critical to optimize the prehospital care of the TBI patient. Ideally, this would be realized by bringing hospital-type care to the accident scene. Given the enormous variability of the early posttrauma period and the generally challenging environment in which care must be delivered, such a concept is not realistic. Indeed, the very concept itself continues to be the topic of raging debate (the "scoop and run" versus "stay and play" controversy). As such, it is expedient to simply select what seem to be the most salient points of prehospital TBI management and address them in an evidence-based fashion.

The goal of initial resuscitation in both adults and children is to prevent

secondary brain injury by restoring oxygenation, ventilation, and perfusion. Resuscitation and stabilization of the cardiovascular and respiratory systems in the field, during transfer, and in the hospital need to be emphasized in an effort to optimize outcome from severe pediatric brain injury.

VI. KEY ISSUES FOR FUTURE RESEARCH

Unfortunately, there is a lack of pediatric studies on the ability of protocols directed at minimizing or preventing hypotensive episodes to improve outcome from TBI. Therefore, the link between the predictive value of hypotension in predicting outcome and the treatment value of preventing hypotension in improving outcome, albeit logical, remains conjectural.

Hypotension

The determination of treatment thresholds for hypotension is not amenable to randomized controlled trials for ethical reasons. As such, it is necessary to address this issue by using large, prospectively collected observational databases that allow analysis of this variable while controlling statistically for confounding variables. It has also been suggested that supranormal blood pressures may be acceptable or even associated with improved outcome in children with severe traumatic brain injury. Further investigation in this area is also warranted.

Given the critical need to minimize or eliminate prehospital hypotensive episodes, randomized controlled trials addressing management protocols are necessary. Study of the timing, amount, and composition of resuscitation fluids to be used is warranted. Given the evidence on the efficacy of in-hospital administration of hypertonic saline plus the adult data supporting its use in the prehospital care of the adult TBI patient, a formal study of hypertonic prehospital resuscitation in pediatric TBI should be considered.

Hypoxia

Given the unclear nature of the pediatric literature on prehospital hypoxia, the first order of research should be to further define the nature of its occurrence and influence on outcome. Studies are needed with sufficient patient populations that have the statistical power to make definitive statements. The level of oxygenation during this period needs to be accurately and repeatedly measured (such as by serial monitoring of peripheral oxygen saturation in the field) to address the influence of thresholds of magnitude and duration of hypoxia. This would allow us to assess the role of prehospital hypoxia on outcome as well as to accurately compare the efficacy of various management methods. Finally, since morbidity rate is generally believed to be more relevant to measuring outcome from hypoxic insults than mortality rate, we need to use functional recovery measures as our dependent variables in such investigations.

The effect of hypercarbia, with or without hypoxemia, on outcome is also not clearly defined and deserves investigation. Potential use of more aggressive oxygenation variables in the resuscitation period deserves further investigation.

Brain-Specific Treatments in the Prehospital Setting

The absence of pediatric literature in this area is striking. Clearly, we need to accomplish quantitative evaluation of various methods of managing the pediatric patient with suspected TBI. Comparative studies of different approaches to patient sedation are fundamental to every aspect of managing such patients. Similar studies regarding the use of hyperventilation and mannitol are also required. Although agent-specific, controlled studies would be optimal, a large, multiple-center prospective observational study might be a reasonable first-order approach.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 4. Resuscitation and Prehospital Brain-Specific Therapies: Strategy A—Resuscitation of Blood Pressure and Oxygenation

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. exp anoxia/ or "hypoxia".mp.
6. exp hypotension/ or "hypotension".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Strategy B—Integration of Brain-Specific Treatments Into the Initial Resuscitation of the Severe Head Injury Patient

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. exp analgesia/ or exp analgesics, opioid/ or exp "hypnotics and sedatives"/ or Midazolam/ or Propofol/ or "sedation".mp.
6. neuromuscular blockade/ or "neuromuscular blockade".mp.
7. exp resuscitation/ or "resuscitation".mp.
8. "ACUTE CARE".mp.
9. exp emergency medical services/ or "prehospital".mp.
10. exp Ambulances/
11. exp intensive care units/
12. intensive care/ or "intensive care".mp.
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 4 and 13
15. limit 14 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
16. limit 15 to english language

Chapter 5. Indications for intracranial pressure monitoring in pediatric patients with severe traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Intracranial pressure monitoring (ICP) is appropriate in infants and children with severe traumatic brain injury (TBI) (Glasgow Coma [GCS] score ≤8).

The presence of open fontanels and/or sutures in an infant with severe TBI does not preclude the development of intracranial hypertension or negate the utility of ICP monitoring.

Intracranial pressure monitoring is not routinely indicated in infants and children with mild or moderate head injury. However, a physician may choose to monitor ICP in certain conscious patients with traumatic mass lesions or in patients for whom serial neurologic examination is precluded by sedation, neuromuscular blockade, or anesthesia.

D. Indications from Adult Guidelines. In the adult guidelines for the management of severe TBI (1), there were sufficient data to support a treatment guideline mandating ICP monitoring in patients with severe TBI. Even though pediatric-specific data only support a recommendation for ICP monitoring as a treatment option, no evidence exists to suggest that monitoring is less important in children than adults.

Monitoring ICP is appropriate in patients with severe head injury with an abnormal admission CT scan. Severe head injury is defined as a GCS score of 3–8 after cardiopulmonary resuscitation. An abnormal CT scan demonstrates hematomas, contusions, cerebral edema, and/or compressed basal cisterns.

Intracranial pressure monitoring is appropriate for patients with severe head injury and a normal CT if two or more of the following features are noted on admission: motor posturing, systemic hypotension, or age >40 yrs.

Intracranial pressure monitoring is not routinely indicated in patients with mild or moderate head injury. However, a physician may choose to monitor ICP in certain conscious patients with traumatic mass lesions or for whom serial neurologic examination is precluded by sedation or anesthesia.

II. OVERVIEW

Published data and consensus practice since the late 1970s suggest that intensive management protocols may reduce the incidence of secondary brain injury after severe TBI and thus improve survival and outcome (2–6). A central feature of such protocols is the monitoring of ICP and medical and/or surgical treatment of intracranial hypertension. Control of ICP within the normal range is intended to maintain adequate cerebral perfusion pressure, oxygenation, and metabolic substrate delivery and to avoid cerebral herniation events. The relative importance of avoiding ICP elevation, *per se*, and reduced cerebral perfusion pressure, is currently uncertain. However, severe perturbations in either value are likely to be adverse and are commonly associated with each other and with poor outcome (2, 5, 7–12). Indications for the treatment of variations in cerebral perfusion pressure are addressed in a separate chapter of these guidelines.

No randomized controlled trial to evaluate the effect on outcome of management of severe TBI with or without ICP monitoring has been conducted in any age group. The obstacles to performing such a study include the ethical concern of not monitoring ICP in control patients and the widely accepted use of ICP monitoring in major pediatric centers involved in TBI research. Although modern, ICP-focused, intensive management protocols have almost unquestionably improved outcomes, these protocols have involved the simultaneous change of a number of other major variables: improved prehospital care, cranial CT imaging for accurate diagnosis of mass lesions, increased use of tracheal intubation and controlled ventilation, more aggressive use of enteral and parenteral nutrition, more active medical management of acute injury, and more widespread availability of formal rehabilitation programs. During this period, ICP monitoring has emerged as an accepted practice without being subjected to a randomized trial. Thus, it is difficult to separate the beneficial or deleterious effects of ICP monitoring, or other efforts to "manage" ICP, from the many other developments in treatment of severe TBI.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 18 potentially relevant studies, 14 were used as evidence for this question (Table 1).

Of note, many studies in this literature specifically exclude children <3 yrs of age and those with head injury resulting from nonaccidental trauma (13).

IV. SCIENTIFIC FOUNDATION

There are two lines of evidence to support the use of ICP monitoring in severe pediatric TBI:

1. Strong evidence supports the association of intracranial hypertension and poor neurologic outcome.
2. ICP monitoring and aggressive treatment of intracranial hypertension are associated with the best reported clinical outcomes.

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Barzilay et al. (14), 1988	In a single-center, case-controlled study, ICP and CPP were monitored in 41 severely head-injured children by using a subarachnoid bolt. Intracranial hypertension was treated with ventilatory and medical interventions.	III	ICPmax was 16 ± 3 in survivors and 54 ± 11 in nonsurvivors. CPPmin was 66 ± 9 in survivors and 6 ± 4 in nonsurvivors.
Sharples et al. (28), 1995	In a single-center, prospective observational study, ICP, CBF, AJVDO$_2$, and CMRO$_2$ were measured in 18 severely head-injured children.	III	In 98% of measurements, raised ICP was associated with low CBF. Patients with good outcome had higher CBF in the first 24 hrs after injury than patients with poor outcome.
Chambers et al. (15), 2000	In a single-center, observational study, 207 adults and 84 children with severe head injury underwent ICP and CPP monitoring.	III	ICPmax predictive of poor (GOS) outcome was >35 mm Hg in adults and children, whereas CPPmin was 55 mm Hg in adults and 45 mm Hg in children.
Michaud et al. (16), 1992	In a single-center, observational study, 51 of 75 children with severe CHI underwent ICP monitoring.	III	94% of children with ICPmax <20 mm Hg survived, whereas only 59% with ICPmax >20 mm Hg survived ($p = .02$). 48% of children with ICP elevation >1 hr survived, compared with 89% of children with ICP elevated for <1 hr. Outcome was also better in children with ICP elevation for <1 hr.
Alberico et al. (17), 1987	In a single-center, prospective, observational study, 330 severely head-injured patients (100 pediatric) underwent ICP monitoring and management.	III	Despite similar ICPs, pediatric patients had better outcomes than adults. This difference was most obvious in patients with ICP <20 mm Hg, but improper subgroup analysis limits the validity of the authors' conclusion that no advantage of young age is present in high ICP groups. Even within the pediatric age group, younger age was associated with significantly better outcome. However, a small group of very young (0–4 yrs) children in this study had poor outcomes.
Kassof et al. (18), 1988	In a single-center, retrospective, observational study, 25 severely head injured children underwent ICP monitoring. Children with elevated ICP were treated with mannitol and, if refractory to mannitol, barbiturates.	III	Children with elevated ICP had an absolute lower survival rate than children with normal ICP, although no statistical analysis is presented.
Eder et al. (19), 2000	In a single-center, retrospective study of 1,108 children with severe head injury, 21 had clinical and radiographic evidence of focal brainstem injury. ICP monitoring data and other factors were compared with outcome.	III	Children with brainstem injury and ICPmax >40 had a significantly higher incidence of death/vegetative state (GOS 1–2) than children with lower ICP (statistical reanalysis of data presented in Table 1 [19]).
Esparza et al. (20), 1985	In a single-center, observational study of 56 severely head-injured children, ICP monitoring, evacuation of mass lesions, hyperventilation, and other medical therapies were used.	III	Children with ICPmax <40 mm Hg had significantly higher rate of "good" outcomes (statistical reanalysis of data presented in Table 2. [20]).
Bruce et al. (27), 1979	In a single-center, observational study, 40 of 80 children with severe TBI underwent ICP monitoring and medical management, emphasizing hyperventilation therapy to control intracranial hypertension.	III	Intracranial hypertension (ICP >20 mm Hg) was markedly more prevalent in children without (80%) than with (20%) spontaneous motor function. 87.5% of children achieved "useful" recovery, and 9% died.
Peterson et al. (25), 2000	In a single pediatric center, 68 children with closed head injury, CT demonstration of diffuse injury and/or mass lesion, and ICP >20 mm Hg were studied retrospectively. These children received intravenous infusion of 3% hypertonic saline as needed to reduce ICP ≤ 20 mm Hg.	III	Treatment effectively lowered ICP in these patients. Three patients died of uncontrolled intracranial hypertension.
Downard et al. (22), 2000	In a retrospective study, 118 brain-injured children who underwent ICP monitor placement within 24 hrs of injury were studied at two urban neurotrauma centers comprising a statewide level I trauma system.	III	In a stepwise logistic regression analysis, ICP >20 mm Hg was significantly associated with an increased risk of death.
Cho et al. (24), 1995	At a single institution, 23 children under 2 yrs of age were treated for abusive head trauma causing severe TBI. Six children with ICP <30 mm Hg were treated with medical therapy alone, and 17 children with ICP >30 mm Hg were treated with either medical therapy or medical therapy plus decompressive craniectomy, in nonrandomized fashion. Decompressive craniectomy effectively reduced ICP.	III	Children with ICP <30 mm Hg and children with ICP >30 mm Hg before treatment with decompressive craniectomy experienced improved survival compared with children with ICP >30 mm Hg treated with medical management alone.

Table 1. (Continued)

Reference	Description of Study	Data Class	Conclusion
Taylor et al. (23), 2001	This single-institution PRCT evaluated 27 children with severe TBI and intracranial hypertension refractory to medical management and ventricular drainage. Children were randomized to continued medical therapy vs. bitemporal decompressive craniectomy.	II	Decompressive craniectomy significantly lowered ICP compared with medical management during the 48 hrs following randomization. There was a strong trend toward improved neurological outcome 6 mos after injury in children who underwent decompressive craniectomy.
Shapiro and Marmarou (21), 1982	Twenty-two children with severe TBI (GCS $\leq$8) were monitored with external ventricular drains.	III	Eighty-six percent of children with severe TBI had ICPs >20 mm Hg. "Diffuse cerebral swelling" on CT scan was 75% specific for the presence of intracranial hypertension.

ICP, intracranial pressure; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; AJVDO$_2$, arterial jugular venous oxidation; GOS, Glasgow Outcome Scale; CT, computed tomography; PRCT, prospective, randomized controlled trial.

Nine studies involving 518 pediatric patients have demonstrated an association between intracranial hypertension and poor neurologic outcome and/or increased mortality rate (14–22). These studies, and their individual ICP thresholds associated with poor outcome (generally >20 mm Hg; see Chapter 6), are listed in Table 1.

Monitoring and aggressive ICP-directed therapy have produced the best historical outcomes in the treatment of severe pediatric TBI. Studies that used three different intervention strategies for ICP control have produced similar and convincing reductions in the expected mortality and/or neurologic morbidity rate. These strategies include decompressive craniectomy (23, 24), hyperosmolar therapy (25), and hyperventilation therapy (26). Each of these strategies is based and depends on accurate, continuous monitoring of intracranial pressure.

Two prospective studies of effective control of refractory intracranial hypertension that used decompressive craniectomy have demonstrated improved neurologic outcome (23, 24). Cho and colleagues (24) performed decompressive craniectomy for medically refractory intracranial hypertension due to abusive head trauma in a cohort of infants and toddlers. They showed improved Children's Outcome Score in the surgical cohort compared with a nearly contemporaneous cohort of nonoperated children from the same institution. Taylor and colleagues (23) performed a prospective, randomized clinical trial of decompressive craniectomy for severe TBI in children aged 1–18 yrs. They showed a significantly reduced ICP in the first 48 hrs after randomization in those patients undergoing surgery, compared with those receiving maximal medical management and ventricular drainage alone. Surgical patients also experienced a strong trend toward improvement in Glasgow Outcome Score 6 months after injury, in this relatively small, single-institution, pilot study.

Peterson et al. (25) reported a retrospective study on the use of continuous infusion of 3% saline in 68 infants and children with severe TBI and refractory intracranial hypertension. Intracranial pressure was monitored and therapy was titrated to control ICP at <20 mm Hg. Although there was no concurrent control group, only three patients died of uncontrolled ICP, and mortality rate (15%) was lower than expected based on trauma severity score (40%).

Bruce et al. (27) studied 85 children with severe TBI by using ICP monitoring and aggressive therapy with hyperventilation and barbiturates to control ICP <20 mm Hg. Again, although there was no concurrent control group, a 9% mortality rate and 87.5% good outcome were achieved.

Although none of these studies achieve class II evidence for long-term outcome, they strongly support the association of ICP monitoring and the effective management of intracranial hypertension with improved outcome. In addition, raised ICP in children may result in secondary brain injury due to alterations in cerebral blood flow physiology (26, 28, 29). Therefore, given the low risk of intracranial pressure monitoring (see Chapter 7), these data suggest a strongly favorable risk/benefit ratio for ICP monitoring in severe pediatric TBI.

The issue of who is at risk for intracranial hypertension is less clear for infants and young children than adults with TBI. Shapiro and Marmarou (21) reported a retrospective evaluation of ICP monitoring in a case series of 22 children with TBI. They found that 86% of children with a GCS $\leq$8 had ICP values >20 mm Hg during the course of their monitoring.

Although GCS and neurologic examination remain the standard for the clinical evaluation of patients with TBI, these may be less sensitive in infants and young children (30, 31). Certain imaging correlates of intracranial hypertension (such as compressed basal cisterns) are also poorly defined and can be misleading in children (21, 32). Combined with a paucity of pediatric-specific studies, this results in limited information about which pediatric TBI patients are at risk for intracranial hypertension and should be monitored. However, given that pediatric head injury patients may suffer late deterioration and death (31), monitoring certain patients with moderate TBI (e.g., those undergoing sedation, neuromuscular blockade, or anesthesia for the management of extracranial injuries) may be appropriate.

The clinical evaluation of an infant with TBI may be difficult, and a normal initial cranial CT does not rule out the possibility of intracranial hypertension (30–32). The presence of open fontanels and/or sutures does not preclude the development of intracranial hypertension (24). Thus, intracranial pressure monitoring can be of significant use in infants suffering from severe traumatic brain injury due to abusive head trauma or other mechanisms.

Two lines of evidence support the use of intracranial pressure (ICP) monitoring as a treatment option in severe pediatric traumatic brain injury (TBI). In addition, guideline level support in the adult literature mirrors the pediatric evidence that ICP monitoring is of clinical benefit in severe TBI.

Key Elements From the Adult Guidelines Relevant to Pediatric TBI

Severely head-injured patients (GCS ≤8) are at high risk for intracranial hypertension (10, 33). The combination of severe head injury and an abnormal head CT scan suggests a high likelihood (53–63%) of raised ICP (12). However, even with a normal admission CT scan, intracranial hypertension may be present (3, 34).

Patients with mild and moderate head injury (GCS 9–15) are less likely to suffer from intracranial hypertension than severely head-injured patients, and therefore the small risk and expense of ICP monitoring may be relatively less justified. Furthermore, serial neurologic examinations are more eloquent in these patients and likely of greater accuracy in monitoring clinically significant changes in neurologic status. However, conscious patients with traumatic mass lesions suggestive of a risk of neurologic deterioration, such as diffuse brain swelling on CT or temporal lobe contusion, may be monitored based on the opinion of the treating physician (4, 32). Inability to perform serial neurologic examinations, because of pharmacologic sedation or anesthesia, may also influence a clinician's decision to monitor ICP in an individual patient (30, 31).

In adults, the presence of two of three adverse factors (systolic hypotension, unilateral or bilateral motor posturing, age >40) predicted a significant rate of intracranial hypertension despite a normal CT scan. Data collected predominantly in adult patients suggest that detection and treatment of intracranial hypertension may protect cerebral perfusion, avoid cerebral herniation, and improve neurologic outcome (5, 10, 32, 33, 35, 36). Thus, the "Guidelines for the Management of [Adult] Severe Head Injury" (1) recommend ICP monitoring in adults with an abnormal CT scan or with two or more of these variables.

Clinical signs of raised ICP are generally associated with a change in the level of consciousness and/or cerebral herniation. Level of consciousness is not measurable in severely head-injured (and thus by definition comatose) patients, and herniation comes after severe and often irreversible brain injury has occurred (37, 38). Direct, physiologic monitoring is thus the most accurate method of determining ICP (38, 39).

Intracranial pressure data allow the management of severe head injury by objective criteria. This is particularly important because many, and perhaps all, medical and surgical measures for the treatment of intracranial hypertension have significant potential adverse consequences (40–42). Thus, ICP monitoring allows the judicious use of interventions such as hyperosmolar therapy, sedatives, paralytics, barbiturates, and ventilator management, with a defined end point that is correlated with clinical outcome. This may avoid potentially harmful, overly aggressive treatment.

In adults, a number of important studies suggest that ICP monitoring and intervention for intracranial hypertension may have a significant salutary effect on survival and outcome after severe head injury. Intensive management protocols including ICP monitoring have lowered mortality rates compared with historical controls and compared with centers in other countries not using monitoring techniques (2, 32, 43, 44). Eisenberg et al. (45) reported that in severely head-injured patients, those in whom ICP could be well controlled with barbiturates had better outcomes than those with refractory intracranial hypertension. Finally, in a small, single-institution study of patients triaged according to the attending neurosurgery call schedule, mortality rate was more than four times higher in nonmonitored than in moni-tored patients with severe head injury (46).

V. SUMMARY

Two lines of evidence support the use of ICP monitoring as a treatment option in severe pediatric TBI. In addition, guideline level support in the adult literature mirrors the pediatric evidence that ICP monitoring is of clinical benefit in severe TBI. Intracranial hypertension may be difficult to diagnose in infants and young children and is associated with decreased survival and poor neurologic outcome. The presence of an open fontanel and/or sutures in an infant with severe TBI does not preclude the development of intracranial hypertension or negate the utility of ICP monitoring. ICP monitoring is not routinely indicated in infants and children with mild or moderate head injury. However, a physician may choose to monitor ICP in certain conscious patients with traumatic mass lesions or in whom serial neurologic examination is precluded by sedation, neuromuscular blockade, or anesthesia.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Definitive evidence of the value of ICP monitoring would require the performance of a prospective, randomized clinical trial of appropriate power. However, it appears unlikely that such a study will ever be carried out. Study of the efficacy of specific, ICP-directed therapies on long-term, age-appropriate, neurologic outcome in infants and children is needed. Further study of the efficacy of ICP-directed therapies in infants and young children with an open fontanel and/or sutures is needed. Similarly, additional studies of ICP monitoring and ICP-directed therapies in infants and young children with abusive head trauma should be conducted.

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See APPENDIX on Next Page

APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 5. Indications for ICP Monitoring

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. intracranial pressure/ or "intracranial pressure".mp.
6. intracranial hypertension/ or "intracranial hypertension".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 6. Threshold for treatment of intracranial hypertension

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Treatment for intracranial hypertension, defined as a pathologic elevation in intracranial pressure (ICP), should begin at an ICP ≥20 mm Hg.

Interpretation and treatment of intracranial hypertension based on any ICP threshold should be corroborated by frequent clinical examination, monitoring of physiologic variables (e.g., cerebral perfusion pressure), and cranial imaging.

D. Indications From Adult Guidelines. There are insufficient data to support a treatment standard for this topic (1).

Treatment for intracranial hypertension should be initiated at an ICP upper threshold of 20–25 mm Hg.

Interpretation and treatment of intracranial hypertension based on any ICP threshold should be corroborated by frequent clinical examination and cerebral perfusion pressure (CPP) data.

II. OVERVIEW

The effect of intracranial hypertension, or pathologically elevated ICP, on outcome after severe head injury in children appears to be related to both the absolute peak and duration of elevated ICP and the inverse relation between ICP and cerebral physiologic variables (e.g., cerebral perfusion and compliance). Quantitative guidelines for intracranial hypertension threshold values are needed for management of elevated ICP in children.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 62 potentially relevant studies, five were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Specific thresholds of ICP for institution of therapy in children with severe traumatic brain injury (TBI) have not been established. However, it is clear that prolonged periods of intracranial hypertension or large increases in ICP are associated with poor outcome as evidenced in the following studies. It should be noted that in none of the cited studies did the authors prospectively address ICP treatment thresholds.

Pfenninger et al. (2) retrospectively reviewed the monitoring of ICP in 24 patients with severe TBI. They used a definition of ICP elevation as "persistently" >20–25 mm Hg. The goal of the treatment regimen they followed was to maintain ICP ≤20 mm Hg and abolish ICP elevations that were >25–30 mm Hg that lasted for >3 mins. They reported that extremely high, sustained ICP (>40 mm Hg) was associated with death ($p < .001$); ICP between 20–40 mm Hg was associated with moderate outcome (one dead, two severely disabled, 13 moderate or good); and ICP <20 mm Hg was associated with good outcome (one severely disabled, three moderate or good).

Esparza et al. (3) performed a retrospective review of 56 pediatric patients with severe TBI (defined as Glasgow Coma Scale score <8 for ≥6 after injury). They used a treatment threshold of ICP >20 mm Hg. Surgical evacuation of mass lesions was performed as needed, but no decompressive craniotomy was done. They found that the group of patients with ICP >20–40 mm Hg had a mortality rate of 28%, whereas the group with an ICP >40 mm Hg had a mortality rate of 100%.

Cho et al. (4) performed a retrospective review of 23 infants (mean age = 5.8 months) with TBI due to abusive head trauma. They found that outcome was worse with ICP >30 mm Hg compared with ICP <20 mm Hg or ICP >30 mm Hg treated with surgical decompression. They suggested that patients with ICP <30 mm Hg may be treated successfully with medical treatment only and that there is a role for decompressive craniotomy in patients with ICP >30 mm Hg.

Two additional studies described physiologic derangements associated with an ICP threshold >20 mm Hg. In a prospective study of 21 pediatric patients (mean age = 8 yrs) with severe TBI (Glasgow Coma Scale score <8), Sharples et al. (5) documented an inverse relation between elevations in ICP >20 mm Hg for ≥10 mins and cerebral blood flow (CBF) in 18 patients with ICP monitoring (r = −.24, p = .009). In only two cases was ICP >20 mm Hg associated with CBF equal to or above the normal range. In 66 simultaneous measurements of ICP and CBF, the authors found that the mean CBF = 0.57 mL·g^{-1}·min^{-1} when the ICP was <20 mm Hg, whereas in 56 measurements the CBF was 0.47 mL·g^{-1}·min^{-1} when the ICP was >20 mm Hg (p = .037). Shapiro and Marmarou (6) reported a retrospective, nonrandom case series of 22 children with TBI and ICP monitoring to determine a predefined "pressure-volume index" (PVI; i.e., a measure of cerebral compliance) produced by bolus withdrawal or injection into a ventriculostomy catheter. They defined intracranial hypertension as either an ICP >20 mm Hg for ≥10 mins or the presence of plateau waves or spot elevations >30 mm Hg in the ICP waveform with noxious stimulation. They found that ICP <20 mm Hg was associated with a PVI >80% of predicted; an ICP 21–40 mm Hg was associated with a PVI 60–80%; and ICP >40 mm Hg correlated with a PVI <60%. They concluded that elevated ICP >20 mm Hg was inversely correlated with PVI, supporting a relationship between intracranial hypertension and impaired cerebral compliance.

Key Elements From the Adult Guidelines Relevant to Pediatric TBI

Initiation of ICP treatment at an upper threshold of 20–25 mm Hg was sup-

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Pfenninger et al. (2), 1983	Retrospective review of 24 patients. Treatment threshold set at ICP persistently elevated >20–25 mm Hg. Severely sustained ICP >40 was associated with death. Moderately sustained or acute ICP elevations were not associated with outcome.	III	Supports using ICP >20–25 mm Hg as treatment threshold.
Esparza et al. (3), 1985	Retrospective review of 56 patients with GCS <8. MVA (n = 40), fall (n = 14), child abuse (n = 2). Treatment protocol called for anti-intracranial hypertensive therapies at ICP >20. Mortality rate was 28% in ICP 20–40 mm Hg group vs. 100% in ICP >40 mm Hg group. Outcome was better in ICP <20 group (27 good, two poor) compared with ICP 20–40 (10 good and four poor) and ICP >40 (0 good and 13 poor).	III	Outcome was better if ICP <20 compared with ICP 20–40. Poor outcome related to ICP >20–40 mm Hg. Suggests that ICP >20 mm Hg is a valid treatment threshold.
Cho et al. (4), 1995	Retrospective, single-center study of outcome following shaken baby syndrome in patients <2 yrs old. Patient groups were as follows: (A) ICP <30 with medical treatment only (n = 6) (B) ICP >30 with medical treatment only (n = 7) (C) ICP >30 with surgical decompressive craniotomy (n = 10). Outcome was worse with ICP >30 mm Hg compared with ICP <20 mm Hg or ICP >30 mm Hg treated with surgical decompression.	III	Outcome was worse with ICP >30 mm Hg compared with ICP <20 mm Hg.
Shapiro and Marmarou (6), 1982	Prospective nonrandom case series of 22 patients. ICP treatment threshold defined as ICP ≥20 × 10 min, plateau waves or spot elevations >30 mm Hg with noxious stimuli, or progressive increases in ICP >20 mm Hg. ICP <20 mm Hg was associated with PVI of >80% of predicted; ICP 21–40 mm Hg was associated with PVI 60–80%; and ICP >40 mm Hg correlated with PVI <60%.	III	Elevated ICP >20 mm Hg is inversely correlated with PVI. Clinical signs of increased ICP >20 mm Hg are not always apparent.
Sharples et al. (5), 1995	Prospective, descriptive study of 18 patients. Treatment threshold used was ICP >20 mm Hg for ≥10 min. Authors found an inverse relationship between CBF and ICP. In only two cases of ICP >20 mm Hg was CBF equal to or greater than the normal range.	III	CBF inversely related to ICP. CBF data support use of ICP treatment threshold of >20 mm Hg to prevent cerebral ischemia.

ICP, intracranial pressure; GCS, Glasgow Coma Scale; MVA, motor vehicle accident; PVI, pressure-volume index; CBF, cerebral blood flow.

ported as a treatment guideline (1). No prospective, randomized clinical trial directly compared ICP treatment thresholds and outcome. The largest study using prospectively collected, observational data, controlling for a large number of confounding prognostic variables, associated the mean ICP, in 5 mm Hg steps, with outcome in a logistic regression model and found 20 mm Hg to be the optimal threshold value predicting poor outcome. Multiple, small, noncontrolled reports suggested a range of 15–25 mm Hg of ICP. Only one prospective, double blind, multiple-center, placebo-controlled study in 73 patients demonstrated improved outcome when ICP could be controlled by using a threshold of 20 mm Hg (7). This study was class II with respect to outcome.

Patients may herniate at intracranial pressures <20–25 mm Hg. However, the likelihood of herniation depends on the location of an intracranial mass lesion. Thus, the choice of any threshold must be closely and repeatedly corroborated with the clinical examination and computed tomography imaging in an individual patient. The "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1) concluded that adequate CPP may be maintained in adults with intracranial pressures of >20–25 mm Hg. Thus, in select cases, a higher limit of acceptable ICP may be chosen as long as an adequate CPP can be maintained.

V. SUMMARY

Current pediatric data support defining intracranial hypertension as pathologically elevated ICP ≥20 mm Hg and a treatment option setting an ICP of 20 mm Hg as an upper threshold above which treatment to lower ICP generally should be initiated. There have been some suggestions that lower values for younger children may be used, although there are no data to support this. Intracranial hypertension with pathologically elevated ICP following severe TBI in children increases morbidity and mortality.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Specific threshold values of ICP for institution of therapy in pediatric age groups need to be clearly defined. Defining age-specific and injury-mechanism-specific ranges for ICP and CPP is vital for determining future treatment recommendations. For example, should a lower ICP treatment threshold of 15–20 mm Hg be used for infants? The critical value of ICP and its interaction with other cerebral physiologic variables are major unanswered questions.

As we recognize the importance of CPP and improve our ability to safely maintain an adequate CPP somewhat independent of ICP, the issue of an absolute value for ICP appears to be most closely related to the risk of herniation, which

> *The critical value of intracranial pressure and its interaction with other cerebral physiologic variables are major unanswered questions.*

seems to vary between patients and within patients over the course of their therapy. A method to estimate this "herniation pressure" needs to be developed, and the range of values where CPP is independent of mean arterial and intracranial pressures needs to be determined.

Large, coordinated, multiple-center, randomized clinical trials are the best means of addressing many of these unanswered issues. A national database for severe TBI in children would be useful and provide important information.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 6. ICP Threshold

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. intracranial pressure/ or "intracranial pressure".mp.
6. intracranial hypertension/ or "intracranial hypertension".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 7. Intracranial pressure monitoring technology

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a technology standard for this topic.

B. Guidelines. There are insufficient data to support a technology guideline for this topic.

C. Options. In pediatric patients who require intracranial pressure (ICP) monitoring, a ventricular catheter or an external strain gauge transducer or catheter tip pressure transducer device is an accurate and reliable method of monitoring ICP.

A ventriculostomy catheter device also enables therapeutic cerebrospinal fluid (CSF) drainage.

D. Indications from Adult Guidelines. Recommendations from the adult guidelines (1) were not based on a level of evidence.

A ventricular catheter connected to an external strain gauge is the most accurate, low-cost, and reliable method of monitoring ICP. It also allows therapeutic CSF drainage. ICP transduction via fiberoptic or strain gauge devices placed in ventricular catheters provides similar benefits but at a higher cost.

Parenchymal ICP monitoring with fiberoptic or strain gauge catheter tip transduction is similar to ventricular ICP monitoring but has the potential for measurement drift.

Subarachnoid, subdural, epidural monitors (fluid coupled or pneumatic) and externally placed anterior fontanel monitors are less accurate.

The overall safety of ICP monitoring devices is excellent, with clinically significant complications (e.g., infection and hematoma) occurring infrequently.

II. OVERVIEW

In patients for whom ICP monitoring is indicated, a decision must be made as to what type of monitoring device to use. The optimal ICP monitoring device is one that is accurate, reliable, and cost-effective and that causes minimal patient morbidity. We reviewed the scientific literature on ICP monitoring in children and adults and propose a ranking based on the currently available technology.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 41 potentially relevant studies, two were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

The scientific discussion of ICP monitoring technology is divided into the following pediatric and adult sections: A. ICP monitoring device accuracy and stability; B. optimal intracranial location of monitor; and C. complications.

A. Intracranial Pressure Monitoring Device Accuracy and Stability. There are no pediatric studies on this topic. In infants, external placement on an open anterior fontanel has been used, but there are no corroborative data on accuracy or stability of the device.

B. Optimal Intracranial Location of Monitor. There are no pediatric studies on this topic.

C. Complications. In a retrospective study of 49 pediatric patients with TBI between 2–16 yrs of age, Gambardella et al. (2) compared the accuracy of Camino catheter measurements of ICP to ventriculostomy catheter measurements. There were 12 ventriculostomy catheters used and 37 intraparenchymal Camino catheters placed. The Glasgow Coma Scale (GCS) scores were as follows: 3 (19%), 4 (8.5%), 5 (12%), 6 (27.5%), 7 (15%), and 8 (10%). The authors found that for patients with GCS between 3 and 4, the Camino catheter measurements averaged 3–4 mm Hg less than the ventriculostomy catheter; for GCS of 4, the Camino averaged 2–3 mm Hg more than the ventriculostomy catheter; and in patients with GCS between 3 and 8, the Camino averaged 1 mm Hg less than the ventriculostomy catheter. For patients studied on the same day and with the same GCS score, there was good correlation between ICP measurements with the Camino vs. the ventriculostomy catheter (r = .73–.89).

Most studies define infection as a positive CSF culture in ventricular and subarachnoid bolt monitors or a positive culture of the intracranial device. A better definition is bacterial colonization of the device rather than infection since there have been no reports in large prospective studies of clinically significant intracranial infections associated with ICP monitoring devices (1). In a prospective uncontrolled case series, Jensen et al. (3) reported complications associated with ICP monitoring technology. They reported no clinically significant infections associated with ICP catheters. However, they studied the incidence of positive bacterial cultures of the catheter tip (i.e., colonization) following removal in 98 children with TBI who received ICP monitoring. Initial placement occurred in the pediatric intensive care unit (54%), emergency department (34%), or operating room (12%). The positive catheter tip culture rate was 7% (all positive for *Staphylococcus aureus*) and did not correlate with where the catheter was initially placed (intensive care unit, n = 3; emergency department, n = 4; operating room, n = 0). The mean duration of catheter placement was 7 days (range, 3–40 days). The average duration of catheters with negative tip cultures was 7.3 days, whereas the duration of those with positive tip cultures was 12.1 days (*p* < .013). However, excluding the one outlier of 40 days, the average duration of those with positive tip cultures was 7.5 days (*p* = .7 compared with those with negative tip cultures). Loss of waveform occurred in 13% of catheters, occurring at a mean of 9.5 days (range, 3–15 days). Finally, in catheters that suffered loss of waveform, the average ICP mean value was 11.1 mm Hg (range, 4–23 mm Hg) greater than measured when the catheter was replaced.

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Gambardella et al. (2), 1993	Retrospective study of 49 patients that evaluated correlation between intraparenchymal Camino and ventriculostomy ICP catheters.	III	Good correlation between ICP measurements with the Camino vs. ventriculostomy catheter (r = .73–.89), with differences ranging from 1 to 4 mm Hg.
Jensen et al. (3), 1997	Prospective uncontrolled case series of 98 patients with 12 ventriculostomy catheters and 37 intraparenchymal Camino catheters placed.	III	Infectious complication rate was 7% (all positive for *Staphylococcus aureus*). Loss of waveform occurred in 13% of catheters occurring at a mean of 9.5 days (range, 4–7 days). Data support low incidence of infection and mechanical failure.

ICP, intracranial pressure.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

A. Intracranial Pressure Monitoring Device Accuracy and Stability. The following information is quoted from the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1).

The Association for the Advancement of Medical Instrumentation has developed the American National Standard for Intracranial Pressure Monitoring Devices in association with a neurosurgery committee (4). The purpose of this standard is to provide labeling, safety, and performance requirements and to test methods that will help ensure a reasonable level of safety and effectiveness of devices intended for use in the measurement of ICP.

According to the Association for the Advancement of Medical Instrumentation's standard, an ICP device should have the following specifications:

Pressure range: 1–100 mm Hg

Accuracy: ±2 mm Hg in range of 0–20 mm Hg

Maximum error: 10% in range of 20–100 mm Hg

Current ICP monitors allow pressure transduction by external strain gauge, catheter tip strain gauge, and catheter tip fiberoptic technology. External strain gauge transducers are coupled to the patient's intracranial space via fluid-filled lines, whereas catheter tip transducer technologies are placed intracranially. External strain gauge transducers are accurate and can be recalibrated, but obstruction of the fluid couple can cause inaccuracy. In addition, the external transducer must be consistently maintained at a fixed reference point relative to the patient's head to avoid measurement error.

Catheter tip strain gauge or fiberoptic devices are calibrated before intracranial insertion and cannot be recalibrated once inserted (without an associated ventricular catheter). Consequently, if the device measurement drifts and is not recalibrated, there is potential for an inaccurate measurement especially if the ICP monitor is used for several days.

There is potential for significant ICP measurement drift with fiberoptic pressure transduction and strain gauge pressure transduction in the parenchymal space. However, adult studies of catheter tip strain gauge ICP devices have demonstrated low or negligible drift over 5 days (1). The accuracy of a pressure transduction device can be assessed by placing the device within the lumen of a ventricular catheter and comparing the fluid-coupled ventricular pressure reading to the device being tested. Catheter tip fiberoptic and strain gauge devices tested in this manner show differences (>±2 mm Hg) compared with ventricular ICP readings. This method of pressure transduction comparison may be erroneous when the ventricular catheter is misplaced or occluded.

B. Optimal Intracranial Location of Monitor. The following information is quoted from the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1).

A pressure transduction device for ICP monitoring can be placed in the epidural, subdural, subarachnoid, parenchymal, or ventricular location.

Historically, ventricular ICP is used as the reference standard in comparing the accuracy of ICP monitors in other intracranial compartments (4). It also has the therapeutic benefit of draining CSF in the event of intracranial hypertension. The potential risks of catheter misplacement, infection, hemorrhage, and obstruction have led to alternative intracranial sites for ICP monitoring.

The following statements ensue from review of the adult and pediatric literature:

- Ventricular pressure measurement is the reference standard for ICP monitoring.
- ICP measurement by parenchymal catheter tip strain gauge pressure transduction or a subdural catheter fluid-coupled device is similar to ventricular ICP. However, some investigators have found that subdural and parenchymal fiberoptic catheter tip pressure monitoring does not always correlate well with ventricular ICP.
- Fluid-coupled epidural devices or subarachnoid bolts and pneumatic epidural devices are less accurate than ventricular ICP monitors. Significant differences in readings have been demonstrated between catheter tip strain gauge ICP devices that are placed in the parenchyma vs. the subdural space.

C. Complications. The following paragraph is abstracted from the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1).

The complication rate for ICP monitoring is low. The most common complications are infection and loss of waveform. There are no pediatric reports documenting the incidence of significant brain injury, hemorrhage, or seizures as a result of ICP monitoring. There are no pediatric data on the use of prophylactic antibiotics to prevent infectious complications. In patients with ventriculostomy catheters who require continuous CSF drainage, ICP cannot be measured simultaneously. Although complications rarely produce long-term morbidity in patients, they can increase cost by requiring replacement of the monitor, and they can give inaccurate ICP readings. Each type of pressure transduction system and intracranial location of the monitor has a profile of potential complications. Calibration, monitoring for infection, and checking fluid coupled devices for ob-

*I*n pediatric patients who require intracranial pressure monitoring, a ventricular catheter and/or an external strain gauge transducer or catheter tip pressure transducer device is an accurate and reliable method of monitoring intracranial pressure.

struction are necessary tasks in maintaining an optimal ICP monitoring system.

V. SUMMARY

In pediatric patients who require ICP monitoring, a ventricular catheter and/or an external strain gauge transducer or catheter tip pressure transducer device is an accurate and reliable method of monitoring ICP. A ventriculostomy catheter device also enables therapeutic CSF drainage. Clinically significant infections associated with ICP devices causing patient morbidity are rare and should not deter the decision to monitor ICP. The incidence of other complications, such as hemorrhage or seizures, is unknown, but the absence of reported incidents in the pediatric literature suggests that the incidence is probably low.

Parenchymal catheter tip pressure transducer devices measure ICP similar to ventricular ICP pressure but have the potential for measurement differences and drift due to the inability to recalibrate. These devices are advantageous when ventricular access is limited or unavailable or if there is obstruction in the fluid couple. There are no credible data (class III or better) on the accuracy of subarachnoid or subdural-coupled devices, epidural ICP devices, or externally placed anterior fontanel devices.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Prospective clinical studies in pediatric patients of the accuracy and complication rate of ventricular and intraparenchymal ICP measuring devices need to be performed. An industry or Food and Drug Administration supported national pediatric registry should be established to collect information on this and other issues in pediatric medicine.

The specification standard for pediatric ICP monitoring should include *in vivo* clinical ICP drift measurement. *In vitro* testing devices do not necessarily reflect clinical performance. Specifications for ICP devices should be reviewed in the context of what data are useful in the management of patients who require ICP monitoring.

A study of simultaneous parenchymal and ventricular ICP measurements using an accurate catheter tip transducer device in children would be useful. We must answer the question: Does parenchymal monitoring in or near a contusion site provide ICP data that improve intracranial pressure management and outcome compared with other sites (including contralateral sites) of ICP monitoring in children?

Recommendations for the use of prophylactic antibiotics, surgical techniques, ICP data collection, monitoring for complications, and timing for removal of ICP monitoring devices in children need to be developed. Further improvement in ICP monitoring technology should focus on developing an ICP device that can provide ventricular CSF drainage and parenchymal ICP measurement simultaneously. This would allow *in situ* recalibration and give accurate ICP measurements in case of fluid obstruction or when CSF is actively drained. Noninvasive measurements of ICP need to be developed.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 7. ICP Monitoring Technology

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. intracranial pressure/ or "intracranial pressure".mp.
6. intracranial hypertension/ or "intracranial hypertension".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 8. Cerebral perfusion pressure

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support treatment standards for this topic.

B. Guidelines. A cerebral perfusion pressure (CPP) >40 mm Hg in children with traumatic brain injury (TBI) should be maintained.

C. Options. A CPP between 40 and 65 mm Hg probably represents an age-related continuum for the optimal treatment threshold. There may be exceptions to this range in some infants and neonates.

Advanced cerebral physiologic monitoring may be useful to define the optimal CPP in individual instances.

Hypotension should be avoided.

D. Indications from the Adult Guidelines. The adult guidelines (1) stated there were insufficient data to support either a treatment standard or guideline. Under *Options,* it stated, "Cerebral perfusion pressure (CPP) should be maintained at a minimum of 70 mm Hg." (1)

II. OVERVIEW

Global or regional cerebral ischemia is an important secondary insult to the acutely injured brain. Grossly, the CPP—defined as the mean arterial pressure minus the intracranial pressure (ICP)—defines the pressure gradient driving cerebral blood flow (CBF), which, in turn, is related to metabolic delivery of essential substrates. The posttraumatic brain has a significant incidence of vasospasm that may increase the cerebral vascular resistance and decrease the CPP, producing ischemia. With the use of continuous monitoring capabilities including invasive blood pressure and ICP equipment, the CPP could be manipulated in an attempt to avoid both regional and global ischemia.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 53 potentially relevant studies, five were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

There is abundant evidence that CBF declines following TBI and may frequently reach the ischemic threshold for brain tissue (2–6). Regional CBF may be even more reduced in the vicinity of intracranial hematomas and contusions (7, 8). There is much debate on how best to measure CBF and at what threshold there is actual tissue ischemia. Cerebral perfusion pressure is relatively easy to measure and appears to correlate well with CBF when measured. A low CPP is highly correlated with poor outcome, but there is less evidence that manipulating the CPP can change eventual neurologic outcome in both adults and children.

There is little quality evidence for the role of CPP in pediatric patients. The comprehensive literature search for this guideline only found one class II study and no class I studies.

A retrospective cohort, class II study collected data on all pediatric TBI patients presenting to both level I pediatric trauma centers in Oregon who received an ICP monitor (118 patients, Glasgow Coma Scale [GCS] 6 $\pm$ 3, age 7.4 $\pm$ 4.6 yrs). By logistic regression methods, the authors found mortality rate significantly associated with a mean CPP <40 mm Hg ($p < .01$) and mean ICP >20 mm Hg ($p < .001$). Mean arterial pressure <70 mm Hg (their definition of "hypotension") was not statistically independently associated with death. They also found no incremental reduction of mortality rate or improved 3-month Glasgow Outcome Scale score associated with mean increases of CPP >40 mm Hg. However, only 60% of patients had documented follow-up at 3 months (9).

Barzilay et al. (10) studied 56 consecutive admissions to their pediatric intensive care unit (PICU) with coma from TBI, central nervous system infections (five cases), and miscellaneous etiologies (ten cases) for at least 6 hrs before admission. Mean arterial pressure and CPP were treated in an uncontrolled fashion, and patients were followed until hospital discharge only. Comparison of survivors and nonsurvivors showed results in Table 2. The difference in minimum CPP is significant at $p < .001$.

Elias-Jones et al. (11) studied 39 consecutive PICU admissions for TBI with an initial GCS ranging from 3 to 11 and an age range of 2 months to 13 yrs (average age 7.8 yrs) who had multiple interventions for ICP >20 mm Hg or CPP <50 mm Hg. They showed that all but one survivor (of total 30) had CPP >40 mm Hg, and CPP was <40 mm Hg in seven of nine fatalities ($p < .00002$, Fisher's exact test). The interventions included hypothermia to 32°C and hyperventilation to a $PaCO_2$ of 3.0–3.5 kPa for all patients. Severe hypocapnia was associated with a worse outcome.

Another retrospective case series of 24 consecutive admissions to a PICU of patients with a GCS <8, average age 6.3 yrs, with ten patients between 1 and 5 yrs of age, showed that all survivors had CPP >50 mm Hg ($p < .005$, Fisher's exact test) (12).

Sharples et al. (13, 14) studied a convenience sample of 17 pediatric patients (2–16 yrs old, average age 7 yrs) with TBI and GCS 3–8 by measuring continuous mean arterial pressures and ICPs and calculating CBF and cerebral vascular resistance by using the nitrous oxide method. The authors found cerebral vascular resistance was proportional to CPP (Pearson r = .32, $p = .0003$) and the relationship was even closer in those patients deemed to have a "good" outcome (i.e., near-normal neurologic function).

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

A large randomized controlled trial of 189 patients with severe TBI (15% with a

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Barzilay et al. (10), 1988	Retrospective analysis of survival at hospital discharge with minimum CPP in 56 patients (41 with severe TBI, five with CNS infections, and ten miscellaneous).	III	CPP 65.5 ± 8.5 mm Hg for survivors vs. 6.0 ± 3.9 mm Hg for nonsurvivors ($p <.001$).
Elias-Jones et al. (11), 1992	Retrospective analysis of neurologic outcome at 2.5 yrs (0.5–5 yrs) post-TBI (GCS 5.5, 3–11) associated with extremes of CPP in 39 patients (average age 7.8 yrs, 2 mos–13 yrs).	III	CPP >40 mm Hg in all but one survivor, <40 mm Hg in seven of nine fatalities ($p <.00002$).
Kaiser and Pfenninger (12), 1984	Retrospective analysis of 24 patients (average age 6.3 yrs) with severe TBI (all GCS <8), 21.5% with ICH, GOS follow-up 2.5 yrs (1.5–4.4 yrs).	III	All survivors with minimum CPP >50 mm Hg ($p < .005$).
Sharples et al. (13), 1995	Retrospective analysis of 17 patients (convenience sample), aged 2–16 yrs (average 7 yrs), neurologic outcome ("good and moderate" vs. "severe and died"). CPP, CBF, and CMRO$_2$ calculated.	III	CVR proportional to CPP (r = .32, $p = .0003$). CVR not related to age, GCS, or time from injury.
Downard et al. (9), 2000	Retrospective cohort study of 118 patients (age 7.4 ± 4.6 yrs) with ICP monitors established within 24 hrs of admission, GCS 6 ± 3, 50% with space occupying lesions, hourly CPP calculations. GOS last recorded in chart.	II	No survivors with mean CPP <40 mm Hg ($p <.01$); no relationship for increments of CPP >40 mm Hg.

CPP, cerebral perfusion pressure; TBI, traumatic brain injury; CNS, central nervous system; ICH, intracranial hemorrhage; GOS, Glasgow Outcome Scale; CBF, cerebral blood flow; CMRO$_2$, cerebral metabolic rate of oxygen; CVR, cerebral vascular resistance; GCS, Glasgow Coma Scale.

Table 2. Comparison of cerebral perfusion pressure (CPP) and intracranial pressure (ICP) in survivors vs. nonsurvivors (10)

	Minimum CPP, mm Hg	Maximum ICP, mm Hg
Survivors	65.5 ± 8.5	16.9 ± 3.1
Nonsurvivors	6.0 ± 3.9	53.7 ± 10.8

gunshot wound) compared ICP-targeted therapy with CBF-targeted therapy that resulted in a CPP >50 mm Hg in the first group and a CPP >70 mm Hg in the second. It showed no difference in 3- or 6-month Glasgow Outcome Scale score, but there was an increased risk of adult respiratory distress syndrome in the second group (15). Another large prospective study of 353 severe TBI patients, with 178 receiving continuous monitoring and management of cerebral oxygen extraction in addition to management of CPP, showed that the additional intervention was associated with better neurologic outcome at 6 months (16). A retrospective study by Changaris et al. (17) in 136 adult patients showed that all patients with a CPP <60 mm Hg on the second day of injury died and more patients with a CPP >80 mm Hg had a better outcome. Another retrospective study of 221 patients followed for a year after TBI also showed better outcomes including mortality rate ($p < .001$) if CPP >80 mm Hg (18). Multiple prospective studies evaluating interventions such as hypothermia, barbiturate coma, and controlling jugu-lar venous oxygen content used CPP >70 mm Hg as a target without directly evaluating this variable alone (19–23). Two studies looked at the relationship of artificially raising the mean arterial pressure in TBI patients with inotropes, and these studies found that this intervention had little effect on the ICP, thereby raising CPP and CBF. The studies were too small to find an effect on ultimate outcome (24, 25). Another small study (n = 21) showed that an increase of CPP from an average of 32 to 67 mm Hg significantly improved brain tissue Po$_2$ but that further increases did not improve this variable (26).

V. SUMMARY

A CPP <40 mm Hg is consistently associated with increased mortality, independent of age. It is unclear whether this value represents a minimal threshold or whether the optimal CPP may be above this in children (e.g., 50–65 mm Hg), based on available data. There are likely to be age-related differences in optimal CPP goals that are indiscernible due to small numbers in these pediatric studies. No study demonstrates that active maintenance of CPP above any target threshold in pediatric TBI is responsible for improved mortality or morbidity.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Controlled, prospective, randomized studies in children are needed to determine optimal CPP levels in various pediatric age groups and mechanisms of injury. The relative importance of ICP and CPP-targeted therapies needs to be assessed by using age-appropriate long-term (>1 yr) functional outcomes.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 8. Cerebral Perfusion Pressure

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. cerebral perfusion pressure.tw.
6. cerebrovascular circulation/ and blood pressure/
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
10. limit 9 to english language

Chapter 9. Use of sedation and neuromuscular blockade in the treatment of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.*

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.*

C. Options. In the absence of outcome data, the choice and dosing of sedatives, analgesics, and neuromuscular blocking agents used in the management of infants and children with severe traumatic brain injury (TBI) should be left to the treating physician. However, the effect of individual sedatives and analgesics on intracranial pressure (ICP) in infants and children with severe TBI can be variable and unpredictable.

D. Indications from Adult Guidelines. The guidelines on the management of adults with severe TBI (1) did not include a specific chapter on the use of sedation, analgesia, or neuromuscular blockade.

In the chapter on initial management (2), it was stated that neuromuscular blocking agents can facilitate mechanical ventilation and management of raised ICP, but their use should be reserved for specific indications. The depth and duration of neuromuscular blockade should be monitored and optimized, respectively.

II. OVERVIEW

Sedatives, analgesics, and neuromuscular blocking agents are commonly used in the management of infants and children with severe TBI. Use of these agents can be divided into two major categories: a) for emergency intubation, and b) for management including control of ICP in the intensive care unit (ICU). The use of

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*As stated by the Food and Drug Administration, continuous infusion of propofol for either sedation or the management of refractory intracranial hypertension in infants and children with severe traumatic brain injury is not recommended.

sedatives, analgesics, and neuromuscular blocking agents for emergency intubation is addressed in chapter 3. This section evaluates use of sedation, analgesia, and neuromuscular blockade during ICU treatment.

Despite their common use in the management of severe TBI in infants and children, sedatives, analgesics, and neuromuscular blocking agents have been subjected to very limited clinical investigation. Most of the medical literature on these agents in pediatric TBI consists of either descriptions of small numbers of children included in adult studies (but not fully described) or case reports—often describing an unanticipated response to administration of a given agent. The lack of high-quality pediatric studies severely limits any conclusions that can be made.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 40 potentially relevant studies, one was used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

A. Sedation and Analgesia. The recommendations on the use of sedatives, analgesics, and neuromuscular blocking agents in this chapter are for patients with a secure airway who are receiving mechanical ventilatory support yielding the desired arterial blood gas values. Sedatives and analgesics are believed to favorably treat a number of important pathophysiologic derangements in severe TBI. They can facilitate necessary general aspects of patient care such as the ability to maintain the airway, vascular catheters, and other monitors. Sedatives and analgesics also can facilitate patient

transport for diagnostic procedures. Sedatives and analgesics also are believed to be useful by mitigating aspects of secondary damage. Pain and stress markedly increase cerebral metabolic demands and can pathologically increase cerebral blood volume and raise ICP.

Studies in experimental models showed that a two- to three-fold increase in cerebral metabolic rate for oxygen accompanies painful or stressful stimuli (3, 4). Noxious stimuli such as suctioning also can increase ICP (5–8). Painful and noxious stimuli and stress also can contribute to increases in sympathetic tone, with hypertension, and bleeding from operative sites (9). However, sedative-induced reductions in arterial blood pressure can lead to cerebral vasodilation and exacerbate increases in cerebral blood volume and ICP. In the absence of advanced monitoring, care must be taken to avoid this complication.

Sedatives and analgesics are used to treat painful and noxious stimuli. They also facilitate mechanical ventilatory support. Other proposed benefits of sedatives after severe TBI include anticonvulsant and anti-emetic actions, the prevention of shivering, and mitigation of the long-term psychological trauma of pain and stress. Prielipp and Coursin (10) described the ideal sedative for patients with severe TBI as one that is rapid in onset and offset, is easily titrated to effect, has well-defined metabolism (preferably independent of end-organ function), neither accumulates nor has active metabolites, exhibits anticonvulsant actions, has no adverse cardiovascular or immune actions, and lacks drug-drug interactions, while preserving the neurologic examination.

Eight studies were identified that addressed the use of sedatives and/or analgesics in severe pediatric TBI. However, none of these reports reached the level of class III data. All either were studies in adults that included a small unstratified

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Vernon and Witte (33), 2000	Prospective, unblinded crossover study of the effect of neuromuscular blockade on oxygen consumption in 20 mechanically ventilated children, six of whom had severe TBI.	II[a]	Neuromuscular blockade reduced oxygen consumption and energy expenditure 8.7 ± 1.7% and 10.3 ± 1.8%, respectively. Although the effect was significant, the magnitude was modest.

TBI, traumatic brain injury.

[a]Class II evidence only for the effect of neuromuscular blockade on oxygen consumption—not on long-term outcome.

number of children or were case reports. The sedatives and analgesics in these studies included narcotics, benzodiazepines, ketamine, and propofol.

Tobias (11) reported that bolus fentanyl (5 μg/kg body weight) produced a spike in ICP in an 11-yr-old child with severe TBI. ICP responded to barbiturate and mannitol administration. Remarkably, this is the only identified report on either fentanyl or morphine use in the management of ICP in pediatric TBI. Albanese et al. (12) studied the effect of sufentanil (1 μg/kg intravenous bolus plus infusion) on ICP in ten comatose patients with severe TBI, including three adolescents. Sufentanil increased ICP 9 ± 7 mm Hg and decreased cerebral perfusion pressure (CPP) 38% after administration. Infusion of the ultra-short-acting narcotic remifentanil controlled refractory ICP in a 16-yr-old child with severe TBI, when hypotension limited propofol use (13).

Cotev and Shalit (14) studied the effect of diazepam in eight patients with severe TBI, including one adolescent. An ∼25% reduction in cerebral metabolic rate for oxygen and cerebral blood flow was seen without an effect on blood pressure. Studies of other commonly used benzodiazepines (midazolam, lorazepam) in pediatric TBI are lacking. Albanese et al. (15) studied the effect of ketamine (1.5, 3, and 5 mg/kg intravenous boluses) on ICP and electroencephalogram in eight patients (including three teenagers) with severe TBI. Surprisingly, bolus doses of ketamine, a sedative agent that has been contraindicated for use in the setting of increased ICP, was associated with a 2–5 mm Hg reduction in ICP.

Spitzfaden et al. (16) reported successful treatment of refractory intracranial hypertension in a 7-yr-old with TBI using continuous infusion of propofol (3–5 mg·kg^{-1}·hr^{-1} for 4 days). Similarly, Farling et al. (17) reported a study on the effect of propofol (intravenous infusion of 1.04–4.97 mg·kg^{-1}·hr^{-1}) in ten comatose patients (including two teenagers) with severe TBI. Propofol infusion (for 24 hrs) produced adequate sedation and no major changes in ICP or CPP. However, a number of reports (in cases not restricted to TBI) suggest that administration of propofol by continuous infusion is associated with an unexplained increase in mortality risk. A syndrome of lethal metabolic acidosis can occur (18–22). "Propofol syndrome" also has been reported in an adult with severe TBI (23). In light of these risks, and with alternative therapies available, continuous infusion of propofol for either sedation or management of refractory intracranial hypertension in severe pediatric TBI is not recommended. The Center for Drug Evaluation and Research (24) of the FDA states, "Propofol is not indicated for pediatric ICU sedation as safety has not been established."

Although there is one report of sedation with infusion of etomidate in TBI that included children (25), lack of age stratification made it impossible to define its effect in the pediatric subgroup. No articles were located that evaluated the use of lidocaine to blunt the response to airway stimulation in children with severe TBI. Finally, barbiturates can be given as sedatives by using doses lower than those required to induce barbiturate coma. The use of high-dose barbiturates in the management of infants and children with severe TBI will be addressed in Chapter 13.

B. Neuromuscular Blockade. Neuromuscular blocking agents have been suggested to reduce ICP by a variety of mechanisms including a reduction in airway and intrathoracic pressure with facilitation of cerebral venous outflow and by prevention of shivering, posturing, or breathing against the ventilator (26). Reduction in metabolic demands by elimination of skeletal muscle contraction also has been suggested to represent a beneficial effect of neuromuscular blockade.

Risks of neuromuscular blockade include the potential devastating effect of hypoxemia secondary to inadvertent extubation, risks of masking seizures, increased incidence of nosocomial pneumonia (shown in adults with severe TBI) (26), cardiovascular side effects, immobilization stress (if neuromuscular blockade is used without adequate sedation and analgesia), and increased ICU length of stay (26, 27). Myopathy is most commonly seen with the combined use of nondepolarizing agents and corticosteroids. Incidence of this complication varies greatly between studies and ranges between 1% and >30% of cases (28–30). Monitoring of the depth of neuromuscular blockade can shorten duration of neuromuscular blockade in the ICU (31).

Two pediatric studies of neuromuscular blocking agents, which were not restricted to children with TBI, suggest that these agents are more commonly used in the management of critically ill infants and children than in adults—as much as five times more common (28, 32). However, only two studies were identified that addressed the use of neuromuscular blocking agents in the setting of severe pediatric TBI (33, 34). One of these reports reached the level of class II data for the effect of neuromuscular blocking agents on systemic oxygen consumption. Vernon et al. (33) performed a prospective, unblinded crossover study of the effect of neuromuscular blockade with vecuronium or pancuronium on total body oxygen consumption in 20 mechanically ventilated children, six of whom had severe TBI. Neuromuscular blockade reduced oxygen consumption and energy expenditure 8.7 ± 1.7% and 10.3 ± 1.8%, respectively. The authors concluded that although neuromuscular blockade reduces oxygen consumption, the degree of reduction is small. No study of the efficacy of specific therapeutic ap-

> **B**ased on recommendations of the Food and Drug Administration, continuous infusion of propofol is not recommended in the treatment of pediatric traumatic brain injury.

proaches to neuromuscular blockade in the treatment of pediatric TBI was identified. Finally, in a study of eight patients (including two adolescents), continuous infusion of doxacurium provided stable neuromuscular blockade without altering ICP or CPP and was less expensive than other commonly used agents (34).

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

In the chapter on initial management (2) in the adult guidelines, it was stated that approaches to sedation and neuromuscular blockade vary widely. There have been no studies on the influence of sedation on outcome from severe TBI; therefore, the decisions on the use of sedation and the choice of sedative agents were left up to the treating physician. Adult guidelines also were not written for the use of neuromuscular blocking agents. However, the initial management section cited one class II study by Hsiang et al. (26) that examined 514 entries in the Traumatic Coma Data Bank and reported an increased incidence of nosocomial pneumonia and prolonged ICU stay associated with early prophylactic use of neuromuscular blockade. It was suggested that use of neuromuscular blocking agents be reserved for specific indications (intracranial hypertension, transport).

V. SUMMARY

There were no studies with sedatives or analgesics providing acceptable evidence for the present report. There was only one study of the use of neuromuscular blockade that qualified as class II,

and that involved the effect of neuromuscular blockade on oxygen consumption only. Until experimental comparisons among specific regimens of these sedative, analgesic, and neuromuscular blocking agents are carried out, the choice and dosing of sedatives and analgesic agents used in the management of infants and children with severe TBI should be left to the treating physician.

Based on recommendations of the FDA, continuous infusion of propofol is not recommended in the treatment of pediatric TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Additional study is needed comparing the various sedatives and analgesics in pediatric patients with severe TBI. Assessments are needed of optimal agents, dosing, duration, and interaction effects with other concurrent therapies. Study of the effect of various sedation strategies on the development and therapeutic intensity level of intracranial hypertension also is needed. Although multiple-center trials assessing the effect of these agents on outcome would be optimal, based on the current dearth of investigation on the use of sedatives and analgesics in pediatric TBI, even case series or small cohort studies would advance the literature. Similarly lacking are studies addressing the important issue of age-related differences and the unique subgroup of infants who are victims of abusive head trauma. The issue of age-related differences may be of particular importance in the area of sedation, since studies in experimental animal models of TBI suggest that some level of synaptic activation is essential to normal development in infancy and that anti-excitotoxic agents may trigger apoptosis in the injured brain (35, 36). Thus, optimal sedation after severe TBI may differ between infants and older children and deserves specific investigation. Finally, the specific role of neuromuscular blocking agents in infants and children with severe TBI also remains to be studied.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 9. Sedation and Neuromuscular Blockade

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. brain ischemia/ or "cerebral ischemia".mp.
6. 4 and 5
7. limit 6 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 10. The role of cerebrospinal fluid drainage in the treatment of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Cerebrospinal fluid (CSF) drainage can be considered as an option in the management of elevated intracranial pressure (ICP) in children with severe closed head injury.

Drainage can be accomplished via a ventriculostomy catheter alone or in combination with a lumbar drain. The addition of lumbar drainage should be considered as an option only in the case of refractory intracranial hypertension with a functioning ventriculostomy, open basal cisterns, and no evidence of a major mass lesion or shift on imaging studies.

II. OVERVIEW

In children with severe traumatic brain injury (TBI) and intracranial hypertension, ventricular CSF drainage is a commonly employed therapeutic modality in conjunction with ICP monitoring. The role of CSF drainage is to reduce intracranial fluid volume and thereby lower ICP. The scientific literature pertaining to CSF drainage in trauma, and in pediatric trauma in particular, was reviewed.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 68 potentially relevant studies, three were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

With the use of the ventriculostomy as a common means of measuring ICP of patients with TBI (see Chapter 7), the potential therapeutic benefits of CSF drainage became of interest. Before the use of the ventriculostomy in TBI, the principal use of CSF drainage was in patients with hydrocephalus, but the ability of this procedure to affect ICP led to its increased use as a therapeutic device.

We found one class III study in children evaluating the use of ventricular drainage in TBI. Shapiro and Marmarou (1) retrospectively studied 22 children with severe TBI—defined as a score ≤8 on the Glasgow Coma Scale (GCS), all of whom were treated with ventricular drainage. Variables measured included ICP, pressure-volume index, and mortality rate. In addition to the finding that draining CSF increased pressure-volume index and decreased ICP, only two neurologic deaths occurred in patients with refractory intracranial hypertension.

Drainage of CSF is not limited to the ventricular route. In response to observations that the ventricles are often small in TBI and that up to 30% of the total compliance of the CSF system is in the spinal axis, a series of articles have addressed the feasibility of using lumbar drains in addition to ventricular drainage. Baldwin and Rekate (2) reported on a series of five children with severe TBI, in whom lumbar drains were placed after failure to control ICP with both ventricular drainage and barbiturate coma. Three children had quick and lasting resolution of raised ICP, two of them with good outcome and one with moderate remaining disability. In the other two cases, there was no effect on ICP and both children died.

Levy et al. (3) reported on the effect of controlled lumbar drainage, with simultaneous ventricular drainage, on outcome in 16 pediatric patients with severe TBI. In two patients ICP was unaffected, and both died. The remaining 14 survived, eight having good outcome, three having moderate disability, and three having severe disability. Although there was no direct outcome study on the use of barbi-turates in this series, the authors proposed that barbiturate coma, and its associated morbidity, could be avoided by the use of lumbar drainage. This statement was based on the fact that in this series not all patients were given barbiturates (five of 16 receiving no barbiturates and six of 16 receiving only intermittent dosing).

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

Following earlier reports of an effect on ICP by drainage of CSF (4), Ghajar et al. (5) performed a prospective study, without randomization, of the effect of CSF drainage in adults with TBI. Treatment was selected by the admitting neurosurgeon and, after evacuation of mass lesions, patients received either ventriculostomies with drainage if ICP exceeded 15 mm Hg along with medical management (group 1) or medical management only (group 2). The medical management consisted of mild hyperventilation to P_{CO_2} = 35 mm Hg, head of bed elevation, normovolemia, and mannitol (although only on admission). Patients in group 2 had no ICP monitor of any kind. The outcome measurements were mortality rate and degree of disability. Mortality ate was 12% in group 1 vs. 53% in group 2. Of the patients in group 1, 59% were living independently at follow-up vs. 20% of group 2.

Fortune et al. (6) studied the effects of hyperventilation, mannitol, and CSF drainage on cerebral blood flow (CBF) in TBI. Twenty-two patients were studied, with a mean age of 24 yrs (range, 14–48). Children were not reported separately. Although patient outcome was not reported, this study established that CSF drainage, hyperventilation, and intermittent mannitol were all effective in reducing ICP. The authors also found that mannitol use increased CBF, CSF drainage had negligible impact on CBF, and hyperventilation decreased CBF.

Ventricular cerebrospinal fluid drainage in severe pediatric traumatic brain injury is supported as a treatment option in the setting of refractory intracranial hypertension; the addition of lumbar drainage in patients showing open cisterns on imaging and without major mass lesions or shift also is supported as a treatment option.

Table 1. Evidence table

References	Description of Study	Data Class	Conclusions
Shapiro and Marmaron (1), 1982	Retrospective series, 22 patients with EVD, ICP/PVI measured.	III	Drainage increased PVI, decreased ICP, deaths only in patients with uncontrolled ICP.
Baldwin and Rekate (2), 1991–1992	Clinical series, five patients with lumbar drain.	III	Three of five survived after lowering ICP.
Levy et al. (3), 1995	Retrospective study, 16 patients with lumbar drain.	III	ICP lowered in 14/16, deaths in two patients with uncontrolled ICP.

EVD, external ventricular drain; ICP, intracranial pressure; PVI, pressure-volume index.

V. SUMMARY

Ventricular CSF drainage in severe pediatric TBI is supported as a treatment option in the setting of refractory intracranial hypertension; the addition of lumbar drainage in patients showing open cisterns on imaging and without major mass lesions or shift also is supported as a treatment option.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Future studies in this area should include the following:

Prospective data collection on the outcome benefits of CSF drainage.

Studies to compare CSF drainage with other therapeutic modalities used in TBI management, such as osmolar therapy or barbiturates.

Work on technical aspects of drain usage, such as continuous vs. intermittent drainage, age-specific use, and use related to mechanism of injury.

Comparison of lumbar drainage with other second-tier therapies, such as decompressive craniotomy.

Study of the potential role of subgaleal drainage in infants.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 10. CSF Drainage

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. lumbar drain$.mp.
6. lumbar shunt$.mp.
7. exp cerebrospinal fluid shunts/
8. *drainage/
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 11. Use of hyperosmolar therapy in the management of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Hypertonic saline is effective for control of increased intracranial pressure (ICP) after severe head injury. Effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale. The minimum dose needed to maintain ICP <20 mm Hg should be used. Pending multiple-center confirmation of effectiveness and lack of toxicity, caution should be exercised in widespread adoption of this therapy.

Mannitol is effective for control of increased ICP after severe traumatic brain injury (TBI). Effective bolus doses range from 0.25 g/kg of body weight to 1 g/kg of body weight.

Euvolemia should be maintained by fluid replacement. A Foley catheter is recommended in these patients to avoid bladder rupture.

Serum osmolarity should be maintained below 320 mOsm/L with mannitol use, whereas a level of 360 mOsm/L appears to be tolerated with hypertonic saline, even when used in combination with mannitol.

The choice of mannitol or hypertonic saline as a first-line hyperosmolar agent should be left to the treating physician.

D. Indications from Adult Guidelines. Most of the pediatric options regarding mannitol, listed previously, mirror those stated in the adult guidelines (1). The adult guidelines only addressed the use of mannitol and not hypertonic saline. Mannitol administration achieved guideline status for the control of intracranial hypertension in the adult document.

II. OVERVIEW

Mannitol is a cornerstone in the management of raised ICP in pediatric and adult TBI. In a recent survey that included 70% of the pediatric intensive care units in the United Kingdom (2), mannitol was used in pediatric TBI in all of the units. Despite this fact, mannitol has not been subjected to controlled clinical trials vs. placebo, other osmolar agents, or other mechanism-based therapies in children. Most of the early and recent study on the use of mannitol focused on the treatment of adults (3–15). Either children were excluded or the composition or outcome of the pediatric tail was not defined (3–18). In a key study, low mean ages were reported, indicating the inclusion of many adolescents and/or children (3). Studies in which the pediatric composition is clearly defined are discussed subsequently. The use of hyperosmolar therapy in the management of infants and children with severe TBI, however, is an area in which there has been much contemporary study. This work, discussed subsequently, has reported on the successful use of hypertonic saline to prevent or treat increased ICP in infants and children with severe TBI.

In constructing an evidence-based document on the use of hyperosmolar therapy in pediatric TBI, one must recognize that the guideline level evidence supporting the use of mannitol in adults relies on studies that often included but did not define the proportion of children. There is a large body of clinical experience using mannitol in infants and children but a limited number of pediatric studies (class III only) that document efficacy of mannitol. In contrast, several recent studies support the use of hypertonic saline in infants and children with severe TBI. However, the use of hypertonic saline has been limited to a small number of centers, and clinical experience with the use of hypertonic saline is limited compared with clinical experience with mannitol.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 46 potentially relevant studies, six were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Intravenous administration of hyperosmolal agents was shown to reduce ICP early in the 20th century (19). Wise and Chater (20) introduced mannitol into clinical use in 1961. Despite widespread use of a number of osmolar agents (mannitol, urea, glycerol) up until the late 1970s (20), mannitol gradually replaced other hyperosmolar agents in the management of intracranial hypertension.

Mannitol can reduce ICP by two distinct mechanisms. Mannitol rapidly reduces ICP by reducing blood viscosity with a resultant decrease in blood vessel diameter (21–24). This occurs as a result of cerebral blood flow (CBF) autoregulation. The level of CBF is maintained, despite a reduction in blood viscosity, through reflex vasoconstriction. Thus, cerebral blood volume and ICP decrease. This mechanism is dependent on intact viscosity autoregulation of CBF, which is linked to blood pressure autoregulation of CBF (21, 23, 24). The effect of mannitol administration on blood viscosity is rapid but transient (<75 mins) (22). Mannitol administration also reduces ICP by an osmotic effect, which develops more slowly (over 15–30 mins), due to the gradual movement of water from parenchyma into the circulation. The effect persists up to 6 hrs and requires an intact blood-brain barrier (25, 26). Mannitol may accumulate in injured brain regions (27), where a reverse osmotic shift may occur—with fluid moving from the intravascular compartment into the brain parenchyma—

Table 1. Evidence table

References	Description of Study	Data Class	Conclusion
James (26), 1980	Retrospective study of 60 patients (1–73 yrs of age) treated with mannitol (0.18–2.5 g/kg per dose) for increased ICP (>25 mm Hg). In 18 patients (12 with TBI, mean age 14 yrs), bolus mannitol was followed by intravenous continuous infusion (6–100 hrs).	III	ICP decreased by ≥10% after 116 of the 120 doses. Bolus doses ≥0.5 g/kg produced an ICP reduction 97% of the time. Other concomitant therapies included dexamethasone, neuromuscular blockade and hyperventilation, barbiturates, and hypothermia, in refractory cases.
Miller et al. (35), 1993	Paired comparison of mannitol (0.5 g/kg) hypnotic (thiopentone 5 mg/kg and/or GABA 60 mg/kg) for refractory ICP >25 mm Hg or >30 mm Hg in 17 patients, including six children (3–17 yrs).	III	Mannitol was superior to hypnotic in five cases; hypnotic was superior to mannitol in three cases; both were effective in five cases; and neither was effective in four cases. Hypnotics were more effective in cases of diffuse TBI; mannitol was effective in focal TBI. Other concomitant therapies included neuromuscular blockade and sedation.
Fisher et al. (52), 1992	Double-blind crossover study comparing 3% saline (1025 mOsm/L) and 0.9% saline (308 mOsm/L) in 18 children with severe TBI. Doses of each agent were equal and ranged between 6.5 and 10 mL/kg in each patient.	III (class II for ICP)	During the 2-hr trial, hypertonic saline was associated with a lower ICP and reduced need for additional interventions (thiopental and hyperventilation) to control ICP pressure. Serum sodium concentration increased ~7 mEq/L after 3% saline.
Khanna et al. (34), 2000	Prospective study of administration of 3% saline (1025 mOsm/L) on a sliding scale to maintain ICP <20 mm Hg in ten children with raised ICP resistant to conventional therapy.	III (class II for ICP)	A significant reduction in ICP spikes and an increase in CPP were observed during treatment with 3% saline. The mean duration of treatment was 7.6 days, and the mean highest serum sodium concentration and osmolarity were 170.7 mEq/L and 364.8 mOsm/L, respectively. Reversible renal failure developed in two patients. Sustained hypernatremia and hyperosmolarity were safely tolerated in pediatric patients.
Simma et al. (53), 1998	Open-randomized prospective study of hypertonic saline (598 mOsm/L) vs. lactated Ringer's administered over the initial 3 days in 35 consecutive children with severe TBI.	III (class II for ICP)	Patients treated with hypertonic saline required fewer interventions than those treated with lactated Ringer's to maintain ICP control. The hypertonic saline treatment group also had shorter length of ICU stay, shorter duration of mechanical ventilation, and fewer complications than the lactated Ringer's-treated group.
Peterson et al. (33), 2000	Retrospect study of the use of a continuous infusion of hypertonic saline (3%) titrated to reduce ICP ≤20 mm Hg in 68 infants and children with closed head injury. Doses of 0.1–1.0 mL·kg^{-1}·hr^{-1} resulting in mean daily dosages between ~11 and 27 mL·kg^{-1}·day^{-1} were used. There was no control group.	III	Three patients died of uncontrolled ICP, and mortality rate was lower than expected based on trauma and injury severity score. No patients developed renal failure. Concomitant therapy included neuromuscular blockade, fentanyl, sedation, hyperventilation, and barbiturates. CSF drainage was rarely used. Hypertonic saline (3%) appeared safe. Central pontine myelinolysis, subarachnoid hemorrhage, or rebound increases in ICP were not observed.

ICP, intracranial pressure; TBI, traumatic brain injury; GABA, γ-aminobutyric acid; CPP, cerebral perfusion pressure; ICU, intensive care unit.

possibly increasing ICP. This phenomenon has been suggested to be most marked when mannitol is present in the circulation for extended periods of time, supporting the use of intermittent boluses (28). Mannitol possesses antioxidant effects (29), but the contribution of this mechanism to its overall efficacy remains unclear.

Mannitol is excreted unchanged in urine, and a risk of the development of acute tubular necrosis and renal failure has been suggested with mannitol administration with serum osmolarity levels >320 mOsm in adults (30–32). However, the literature supporting this finding is limited in scope and was generated at a time when dehydration therapy was common. A euvolemic hyperosmolar state generally is targeted with contemporary care. Much higher levels of serum osmolarity (365 mOsm) appear to be well tolerated in children when induced with hypertonic saline (33, 34). It is unclear if this threshold for complications with mannitol results from concomitant dehydration, the use of mannitol rather than hypertonic saline, or differences between adults and children in their susceptibility to nephrotoxicity. As stated in the adult guidelines, few data exist supporting the concomitant use of diuretics and mannitol to reduce ICP (30).

James (26) carried out a retrospective study of 60 patients (1–73 yrs of age) treated with intravenous mannitol (0.18–2.5 g/kg per dose) for increased ICP (>25 mm Hg). Although cited as class III evidence in the adult guidelines (30), this study included a large number of children. After bolus dosing, ICP decreased by ≥10% for 116 of the 120 doses. Bolus doses of 0.25 g/kg, 0.5 g/kg, and ≥1.0 g/kg reduced ICP in 25%, 78%, and 98% of cases, respectively. This contrasts the work of Marshall et al. (4), who reported equivalence for doses between 0.25 and 1.0 g/kg in adults. The mean time for the return of ICP to baseline was 196 mins, with the shortest reduction being 40 mins. Other concomitant therapies used for patient management in this study included dexamethasone, neuromuscular blockade and hyperventilation, barbitu-rates, and/or hypothermia, in refractory cases.

Miller et al. (35) reported a comparison of mannitol (0.5 g/kg) vs. a hypnotic (thiopentone 5 mg/kg and/or gamma hydroxyl butyrate 60 mg/kg) for refractory ICP (>25–30 mm Hg in 17 patients, including six children, 3–17 yrs of age). Response to therapy was defined in each patient in the study, allowing individual assessment of children. Mannitol was found to be superior to the hypnotic in five cases, the hypnotic was superior to mannitol in three cases, and both were effective in five cases. All of the children responded to either or both agents. Hypnotics were more effective in cases of diffuse TBI, whereas mannitol was effective in focal TBI, but the sample size in this study was limited.

In other studies with exclusively pediatric patients (36, 37), mannitol represented a key component of therapy or even defined a specific subgroup; however, the specific effect of mannitol on ICP or outcome was not reported. In contrast, Bruce and coworkers (38) sug-

gested restricted mannitol use in the 1980s and 1990s. Based in part on the suggested hyperemic response to TBI in children (39) and the possible increase in cerebral blood volume with mannitol administration (when pressure and viscosity autoregulation are defective), it was proposed that mannitol administration carried special risk in pediatric patients with diffuse cerebral swelling early after TBI. The authors recommended against the use of mannitol in the absence of a high probability of mass lesion. Since recent studies showed that early posttraumatic CBF generally is reduced, rather than increased, in infants and children (40), this hypothetical risk of mannitol administration in pediatric patients should not *a priori* dissuade clinicians from administration in the initial 48 hrs.

In the initial description in 1919 of the reduction in ICP by intravenous administration of hyperosmosal agents, hypertonic saline was the agent used (19). The use of hypertonic saline in the treatment of increased ICP, however, failed to gain clinical acceptance. Resurgence in interest in this treatment for raised ICP resulted from the report of Worthley et al. (41), who described two cases in which hypertonic saline (small volumes of an extremely hypertonic solution, ~29% saline) reduced refractory ICP elevations. One of those cases involved treatment of a 17-yr-old boy with TBI. In the last decade, numerous laboratories have studied the use of small volume hypertonic saline in resuscitation of hemorrhagic shock with or without TBI in experimental models and in humans (42–45). These studies are summarized in several recent reviews (46, 47).

Like mannitol, the penetration of sodium across the blood-brain barrier is low (46). Sodium thus shares both the favorable rheologic and osmolar gradient effects involved in the reduction in ICP by mannitol. Hypertonic saline also exhibits several theoretical beneficial effects including restoration of normal cellular resting membrane potential and cell volume (48, 49), stimulation of atrial natriuretic peptide release (50), inhibition of inflammation (reviewed in Ref. 46), and enhancement of cardiac output (51). Possible side effects of hypertonic saline include rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage (reviewed in Ref. 46).

Hypertonic saline has been the subject of considerable investigation with three class II studies (for ICP) and one class III

study in >130 pediatric patients with severe TBI. It should be pointed out that none of these studies produced class II data demonstrating a beneficial effect on long-term outcome.

Fisher et al. (52) carried out a double-blind crossover study comparing 3% saline and 0.9% saline in 18 children with severe TBI. Bolus doses of each agent were equal and ranged between 6.5 and 10 mL/kg. During the 2-hr trial, serum sodium concentration increased about 7 mEq/L, and hypertonic saline was associated with a lower ICP and reduced need for additional interventions. Concomitant therapies used for patient management in this study included thiopental, dopamine, mannitol, and hyperventilation. Cerebrospinal fluid drainage was not used.

Khanna et al. (34) reported a prospective study with administration of 3% saline (514 mEq/L) on a sliding scale to maintain ICP <20 mm Hg in ten children with increased ICP resistant to conventional therapy. The maximal rate of increase in serum sodium was 15 mEq·L^{-1}·day^{-1}, and the maximal rate of decrease in serum sodium was 10 mEq·L^{-1}·day^{-1}. A reduction in ICP spikes and an increase in cerebral perfusion pressure were seen during treatment with 3% saline. The mean duration of treatment was 7.6 days, and the mean highest serum sodium concentration and osmolarity were 170.7 mEq/L and 364.8 mOsm/L, respectively. The maximum serum osmolarity in an individual patient was 431 mOsm/L. Sustained hypernatremia and hyperosmolarity were generally well tolerated in the children. Two patients, both with sepsis and/or multiple organ failure, developed acute renal failure. Both received continuous venovenous hemofiltration and recovered renal function.

Simma et al. (53) carried out an open randomized prospective study of hypertonic saline (598 mOsm/L) vs. lactated Ringer's solution administered over the initial 3 days in 35 children with severe TBI. Patients treated with hypertonic saline required fewer interventions (including mannitol use) to control ICP than those treated with lactated Ringer's solution. Patients in the hypertonic saline treatment group also had shorter length of intensive care unit stay, shorter duration of mechanical ventilation, and fewer complications than the lactated Ringer's-treated group.

Peterson et al. (33), reported a retrospective study on the use of a continuous infusion of 3% saline titrated to reduce ICP to ≤20 mm Hg in 68 infants and children with TBI. The mean daily doses of hypertonic saline over a 7-day period ranged between 11 and 27 mL·kg^{-1}·day^{-1}. There was no control group, but only three patients died of uncontrolled ICP, and mortality rate was lower than expected based on Trauma and Injury Severity Score categorization. No patient with a serum sodium concentration >180 mEq/L had a good outcome. No patients developed renal failure. Concomitant therapies included sedation, neuromuscular blockade, mannitol, hyperventilation, and barbiturates, but cerebrospinal fluid drainage was used in only three children. The mean daily dose of mannitol was 1–2 g·kg^{-1}·day^{-1}. Hypertonic saline appeared to be safe. Rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage were not seen.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

Based on an evidence table in the adult guidelines (30) (two class I and five class II studies), mannitol was deemed to be effective for controlling increased ICP after severe TBI, with effective doses ranging from 0.25 g/kg to 1 g/kg of body weight. Limited data in adults suggest that intermittent boluses may be more effective than a continuous infusion. Several key studies were cited. Schwartz et al. (3) carried out a randomized comparison of mannitol vs. barbiturates in 59 adults with severe TBI. Cerebral perfusion pressure was better maintained in the mannitol-treated group. Gabb et al. (54) and Rosner and Coley (11) reported similar effects. Fortune et al. (14) compared mannitol, ventriculostomy drainage, and hyperventilation to control ICP in 22 adults. Mannitol was the most effective. Use of mannitol for TBI recently was subjected to Cochrane review, and no conclusion could be reached regarding efficacy vs. placebo or any other therapy (55).

V. SUMMARY

Two class III studies support the use of mannitol in pediatric TBI. Neither of these studies included exclusively pediatric patients. One must thus weigh the value of long-standing clinical acceptance and safety of a therapy (mannitol) that

> *One must thus weigh the value of long-standing clinical acceptance and safety of a therapy (mannitol) that has limited evidentiary support (two class III studies) of its efficacy against a newer therapy (hypertonic saline) with a limited clinical experience but reasonably good performance in contemporary clinical trials (three class II studies for intracranial pressure and one class III study).*

has limited evidentiary support (two class III studies) of its efficacy against a newer therapy (hypertonic saline) with a limited clinical experience but reasonably good performance in contemporary clinical trials (three class II studies for ICP and one class III study). Bolus administration of mannitol or continuous infusion of 3% saline is supported. Thus, in pediatric TBI, there is guideline-level support for hypertonic saline to treat increased ICP but limited clinical experience. In contrast, there is only class III evidence for mannitol, despite long-standing clinical acceptance. Until one or more direct comparisons between these two therapies are carried out in infants and children with severe TBI, the choice of either mannitol or hypertonic saline in the management of pediatric TBI is a matter of physician preference.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Additional investigation is needed comparing mannitol administration with hypertonic saline, particularly studies evaluating long-term neurologic outcome. Similarly, study of the use of more aggressive hyperosmolar therapy with other second-tier therapies is needed, including investigation of the prevention of intracranial hypertension by continuous infusion of hypertonic saline vs. treatment in response to spikes. Documentation of the effect of mannitol in studies restricted to infants and children is needed. Similarly lacking are studies in victims of child abuse. Despite the overall quality of the investigations assessing the effect on ICP, the use of hypertonic saline has been limited to a small number of pediatric centers, and a number of factors involved in patient management, such as the use of concomitant therapies like cerebrospinal fluid drainage and the extent of use of specific second-tier therapies, varies greatly between centers. Additional study is needed. Optimal dosing and better definitions of treatment threshold are needed for the development of nephrotoxicity, rebound intracranial hypertension, central pontine myelinolysis, and other complications with mannitol and hypertonic saline.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 11. Hyperosmolar Therapy

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. hyperosmolar therapy.mp.
6. hyperosmolar treatment.mp.
7. Fluid therapy/ or "fluid therapy".mp.
8. saline solution, hypertonic/
9. osmolar concentration/
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10
12. limit 11 to (human and english language)
13. limit 12 to (infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
14. from 13 keep 1–13

Chapter 12. Use of hyperventilation in the acute management of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Mild or prophylactic hyperventilation ($Paco_2$ <35 mm Hg) in children should be avoided.

Mild hyperventilation ($Paco_2$ 30–35 mm Hg) may be considered for longer periods for intracranial hypertension refractory to sedation and analgesia, neuromuscular blockade, cerebrospinal fluid drainage, and hyperosmolar therapy.

Aggressive hyperventilation ($Paco_2$ <30 mm Hg) may be considered as a second tier option in the setting of refractory hypertension. Cerebral blood flow (CBF), jugular venous oxygen saturation, or brain tissue oxygen monitoring is suggested to help identify cerebral ischemia in this setting.

Aggressive hyperventilation therapy titrated to clinical effect may be necessary for brief periods in cases of cerebral herniation or acute neurologic deterioration.

D. Indications from the Adult Guidelines. The adult guidelines recommended (1) at the level of a treatment standard that in the absence of increased intracranial pressure (ICP), chronic prolonged hyperventilation therapy ($Paco_2$ of ≤25 mm Hg) should be avoided after severe TBI. At the level of a treatment guideline, it was recommended that prophylactic hyperventilation ($Paco_2$ ≤35 mm Hg) therapy during the first 24 hrs after severe TBI should be avoided because it can compromise cerebral perfusion during a time when CBF is reduced.

It was recommended as a treatment option that hyperventilation therapy may be necessary for brief periods when there is acute neurologic deterioration or for longer periods if there is intracranial hypertension refractory to sedation, paralysis, cerebrospinal fluid drainage, and osmotic diuretics. Jugular venous oxygen saturation, arterial jugular venous oxygen content differences, brain tissue oxygen monitoring, and CBF monitoring may help to identify cerebral ischemia if hyperventilation, resulting in $Paco_2$ values <30 mm Hg, is necessary.

II. OVERVIEW

Aggressive hyperventilation therapy has been used in the management of severe pediatric TBI for the rapid reduction of ICP since the 1970s. In an uncontrolled study, Bruce et al. (2) used a protocol that included aggressive hyperventilation and reported very good outcomes. This approach was based on the assumption that hyperemia was common after pediatric TBI. Hyperventilation therapy also was thought to benefit the injured brain through a variety of mechanisms including reduction of brain acidosis (3), improvement of cerebral metabolism (4), restoration of blood pressure autoregulation of cerebral blood flow (5), and increasing perfusion to ischemic brain regions (local inverse steal) (6).

More recent pediatric studies have shown that hyperemia is uncommon and also have raised concerns about the safety of hyperventilation therapy. Study of the effect of hyperventilation in children has focused on assessment of cerebral physiologic variables. The effect of hyperventilation therapy on outcome in infants and children with severe TBI has not been directly compared with other therapies such as hyperosmolar agents, barbiturates, hypothermia, or early decompressive craniectomy.

Hyperventilation reduces ICP by inducing hypocapnia. This leads to cerebral vasoconstriction and a reduction in CBF. This is accompanied by a reduction in cerebral blood volume, resulting in a decrease in ICP. However, hyperventilation is associated with a risk of iatrogenic ischemia. In an experimental model, Muizelaar et al. (7) reported that the vasoconstrictor effect of hyperventilation was sustained for a period of <24 hrs. Chronic hyperventilation depletes brain tissue interstitial bicarbonate buffering and causes cerebral circulation to become hyper-responsive to subsequent increases in $Paco_2$. In addition, the respiratory alkalosis that accompanies hyperventilation causes a left shift of the hemoglobin-oxygen dissociation curve, which may impair delivery of oxygen to tissue.

The assumption of benefit from hyperventilation recently has been challenged. Recent clinical studies in mixed adult and pediatric populations also have demonstrated that hyperventilation may decrease cerebral oxygenation and may induce brain ischemia (8–11). After TBI, the CBF response to changes in $Paco_2$ can be unpredictable and should be specifically monitored.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 20 potentially relevant studies, two were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Diffuse cerebral swelling is a common finding in pediatric patients with severe TBI (12, 13). Increased cerebral blood volume and CBF had been considered to be the unique cause of this diffuse swelling, and raised ICP in children and aggressive hyperventilation was advocated (14). In the classic study by Bruce et al. (2), 36 of 76 children with severe TBI were found to have diffuse cerebral swelling on CT scan. Six patients, ages 14–21

Table 1. Evidence table

References	Description of Study	Data Class	Conclusion
Skippen et al. (22), 1997	Prospective cohort, 23 children with isolated severe TBI, GCS <8. Ages 3 mos to 16 yrs, mean 11 yrs. $Paco_2$ was adjusted by minute ventilation to >35, 25–35, and <25 torr. Measured CBF, $C(a–j)O_2$, $CMRO_2 = C(a–j)O_2 \times CBF$. Follow-up GOS 6 mos post-ICU discharge.	II	Severe TBI produced modest decrease in CBF, larger decrease in cerebral oxygen consumption. Hyperemia was uncommon, but measured CBF rates were above metabolic requirements of most. As $Paco_2$ reduced, ICP decreased and CPP increased. However, in almost all patients, CBF decreased.
Stringer et al. (19), 1993	Nonrandomized selected series of case studies. Twelve patients referred for CBF measurement. Three were children with head trauma and coma, ages 1 mo, 6 yrs, and 8 yrs. Xenon-enhanced CT scans. Measured ICP, CPP, MAP, $ETco_2$, XeCT, CBF.	II	Hyperventilation-induced ischemia occurs and affects both injured and apparently intact areas of brain tissue.

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; CBF, cerebral blood flow; $C(a–j)O_2$, cerebral arteriojugular venous oxygen content difference; CMRO, cerebral metabolic rate; ICU, intensive care unit; CT, computed tomography; ICP, intracranial pressure; CPP, coronary perfusion pressure; MAP, mean arterial pressure; $ETco_2$, end-tidal CO_2; XeCT, xenon-enhanced computed tomography.

yrs, were found to have CBF that was normal or above normal. In three patients, CBF decreased back to control levels after diffuse swelling had resolved. Consequently, aggressive hyperventilation ($Paco_2$ 23–25 mm Hg) was advocated and mannitol was discouraged.

There are now data to suggest that hyperemia is not as common as previously thought (15). In a series of 80 normal, unanesthetized children, CBF ranged from 40 mL·100 g^{-1}·min^{-1} in the first 6 months of life to a peak of 108 mL·100 g^{-1}·min^{-1} at age 3–4 yrs, declining to 71 mL·100 g^{-1}·min^{-1} after age 9 yrs. Similarly, Chiron et al. (16) demonstrated that CBF ranged from about 50 mL·100 g^{-1}·min^{-1} in normal neonates to a peak of 71 mL·100 g^{-1}·min^{-1} at 5 yrs. After age 19, CBF gradually decreased to adult levels. Thus, posttraumatic CBF may not be greater than normal in children. However, caution should be exercised in interpreting these studies because techniques used to measure CBF differed between reports.

Adelson et al. (17) studied 30 children with severe TBI, all <8 yrs of age. Seventy-seven percent had CBF <20 mL·100 g^{-1}·min^{-1} on admission. Children were treated with a protocol including mild (Pco_2 32–35 mm Hg) hyperventilation and barbiturate coma (60%). CBF was highest at 24–48 hrs (59.6 ± 4.5 mL·100 g^{-1}·min^{-1}) and decreased (<50 mL·100 g^{-1}·min^{-1}) after 3 days. Any child with global CBF of 20 mL·100 g^{-1}·min^{-1} or less at any time had a poor outcome. CBF of >55 mL·100 g^{-1}·min^{-1} was associated with a higher proportion of children with a good outcome.

Muizelaar et al. (18) studied 32 children with severe TBI (age 3–18 yrs). The average CBF was only 44 ± 22 mL·100 g^{-1}·min^{-1}, which is considerably lower than the average of 68 ± 4 mL·100 g^{-1}·min^{-1} found in four normal unanesthetized children. No correlation was found between CBF and ICP.

Although the effect of hyperventilation on long-term outcome has not been directly addressed in pediatric TBI, several reports have described the effects of hyperventilation on CBF and brain physiology. Stringer et al. (19) studied local CBF and vascular reactivity before and after hyperventilation in 12 patients including three children with severe TBI. Hyperventilation-induced blood flow reductions affected both injured and apparently intact areas of the brain and were not reflected by ICP measurement.

Sharples et al. (20) investigated CBF, arterial jugular venous oxygen difference, and cerebral metabolic rate in 21 children with TBI. No fundamental difference between adults and children in the pathophysiologic response of CBF to severe TBI was found. Absolute cerebral hyperemia was uncommon. Raised ICP was associated with low, rather than increased, CBF. Cerebral metabolic rate was initially normal in 81% of children with TBI. These data do not support the hypothesis that ICP increases as a result of excessive CBF in children with TBI. Based on this study, and on a subsequent study of cerebral vascular reactivity (21), the authors recommended maintaining a normal $Paco_2$.

Skippen et al. (22) found that hyperemia was uncommon in children with severe TBI. However, CBF rates remained above the metabolic requirements of most children studied. A modest decrease in CBF and a much larger decrease in cerebral oxygen consumption were found at baseline. As $Paco_2$ was reduced with hyperventilation, CBF was decreased in almost all patients despite decreased ICP and increased cerebral perfusion pressure. A clear relationship between hypocarbia and frequency of cerebral ischemia was seen. The frequency of regional ischemia (CBF <18 mL·100 g^{-1}·min^{-1}) was 28.9% during normocapnia and increased to 73.1% for $Paco_2$ <25 mm Hg.

The effect of hyperventilation therapy on outcome of infants and children with severe TBI has not been directly compared with other therapies such as hyperosmolar agents, barbiturates, hypothermia, or early decompressive craniectomy. Surprisingly, outcome data reported by Bruce et al. (2) in the late 1970s, when aggressive hyperventilation ($Paco_2$ 20–25 mm Hg) represented the cornerstone of therapy for pediatric TBI (5), has not been surpassed by contemporary protocols and only rarely equaled (23). Hyperventilation may have unique advantages as a therapy in severe pediatric TBI; however, it can only be supported as a second tier therapy based on the current evidence.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

The adult guidelines (1) conclude that prophylactic hyperventilation ($Paco_2$ <35 mm Hg) therapy during the first 24 hrs after severe TBI should be avoided be-

cause it can compromise cerebral perfusion during a time when CBF is already reduced. The guidelines (1) strongly contend that chronic prolonged hyperventilation therapy ($Paco_2$ <25 mm Hg) should be avoided after severe TBI in the absence of increased ICP. It was emphasized that the preponderance of the physiologic literature concludes that hyperventilation during the first few days following severe TBI, whatever the threshold, is potentially deleterious in that it can promote cerebral ischemia.

Specifically, CBF during the first day after injury is less than half that of normal individuals (18, 24–31). During the first 24 hrs after injury, there is a direct correlation between CBF and Glasgow Coma Scale score or outcome (24, 29). Hyperventilation reduces CBF (22, 32–34) even further but does not consistently reduce ICP (35, 36) and may cause loss of autoregulation (37). Aggressive hyperventilation may cause arterial jugular venous oxygen and CBF to approach ischemic levels.

In a prospective randomized clinical trial by Muizelaar et al. (8), 77 severe TBI patients were randomized to a group treated with chronic prophylactic hyperventilation ($Paco_2$ of 25 ± 2 mm Hg) or to a group kept relatively normocapneic ($Paco_2$ of 35 ± 2 mm Hg). At 3 and 6 months after injury, patients with initial Glasgow Coma Scale motor scores of 4–5 in the hyperventilation group had a significantly worse outcome than did patients in the normocapneic group. Statistically significant differences between the two groups were not found at 1 yr after injury; this was attributed to a type II statistical error since substantially fewer patients were available for 1-yr follow-up.

V. SUMMARY

Hyperemia may not be as common in severe pediatric TBI as previously reported. Hyperventilation can reduce CBF to potentially ischemic levels. Additionally, the cerebrovascular response to hyperventilation can be extremely variable following TBI. Studies in children with severe TBI raise the concern that the toxicity of hyperventilation may be similar to the toxicity that has been demonstrated in adults and related to adverse outcome. Unfortunately, the precise relationship between hyperventilation and outcome has not been studied in children with severe TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Studies to identify subgroups of patients who might benefit from hyperventilation are needed.
- Studies are needed to address the timing and duration of the optimal use of hyperventilation.
- Studies to determine the optimal monitoring technique of patients undergoing hyperventilation are lacking.
- Studies are needed to address the influence of age on the response to hyperventilation
- The effects on long-term outcome should be addressed in all aspects of research on hyperventilation. Hyperemia may not be as common in severe pediatric traumatic brain injury as previously reported.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 12. Hyperventilation

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. brain ischemia/ or "cerebral ischemia".mp.
6. 4 and 5
7. limit 6 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 13. The use of barbiturates in the control of intracranial hypertension in severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. High-dose barbiturate therapy may be considered in hemodynamically stable patients with salvageable severe head injury and refractory intracranial hypertension.

If high-dose barbiturate therapy is used to treat refractory intracranial hypertension, then appropriate hemodynamic monitoring and cardiovascular support are essential.

D. Indications from Adult Guidelines. The adult guidelines (1) recommend consideration of high-dose barbiturate therapy in "hemodynamically stable patients with salvageable severe TBI and intracranial hypertension refractory to maximal medical and surgical intracranial pressure-lowering therapy" as a guideline.

II. OVERVIEW

It is estimated that 21–42% of children with severe traumatic brain injury (TBI) will develop intractable elevated intracranial pressure (ICP) despite medical and surgical management (3–8). The reported mortality rates are 29–100% when the ICP is >40 mm Hg despite therapy to lower ICP.

The ICP-reducing and direct neuroprotective properties of barbiturates have prompted the investigation of two approaches for their use in the management of patients with severe traumatic brain injury: a) prophylactic administration early after injury, and b) use in the treatment of refractory ICP.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 19 potentially relevant studies, two were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

High-dose barbiturates are known to reduce ICP; however, side effects have limited their use to cases refractory to first-line therapies (4, 9, 10). Barbiturates appear to exert their ICP-lowering effects through two distinct mechanisms: suppression of metabolism and alterations in vascular tone (11–13). Barbiturates can lower resting cerebral metabolic rate for oxygen by about 50% (11). When cerebral blood flow and cerebral blood volume are coupled to regional metabolic rate, they are also decreased. This mechanism mediates the observed beneficial effects of barbiturates on ICP and cerebral perfusion pressure. However, Cruz (14) reported that some patients treated for intractable ICP with barbiturate coma developed jugular venous oxygen saturation levels <45%, which was associated with a significantly worse outcome compared with patients with higher jugular venous oxygen saturations. This suggested that in some patients, barbiturate coma induced oligemic hypoxia. Cruz included teenagers and adults; however, the results of the teenagers were not separately reported. Barbiturates confer additional direct neuroprotective effects independent of their ICP-lowering properties, such as inhibition of free radical-mediated lipid peroxidation or membrane stabilization (11).

Few studies have evaluated barbiturate pharmacokinetics and pharmacodynamics in children with head injury (15–18). Clearance appears to vary widely and may be increased with duration of therapy (18). Barbiturate serum levels are poorly correlated with electrical activity (16, 17). Monitoring of electroencephalographic patterns for burst suppression is thought to be more reflective of therapeutic effect than measuring serum drug levels (11, 13). Near-maximum reduction in cerebral metabolism and cerebral blood flow occurs when burst suppression is induced (9, 13).

Barbiturates suppress metabolism; however, there is insufficient information about comparative efficacy to recommend one barbiturate over another, except in relation to their particular pharmacologic properties. The use of both pentobarbital and thiopental has been reported.

Prophylactic Use of Barbiturates

There are no published studies of prophylactic barbiturate use in children with severe TBI. The "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1) reported on two randomized clinical trials that examined early prophylactic administration of barbiturates. Neither study demonstrated clinical benefit (19, 20). Schwartz et al. (20) did not define the lower age limits in their study, but the mean patient age suggests that children were included. Ward et al. (21) included adolescents over the age of 12 yrs; however, they did not separately report the effects of the barbiturate therapy among the children. Ward et al. (21) reported that 54% of barbiturate-treated subjects developed hypotension—defined as a systolic blood pressure <80 mm Hg—compared with 7% of controls.

Refractory Intracranial Hypertension

Use of barbiturates to treat elevated ICP in children with severe head injury has been reported since the 1970s (22). Marshall et al. (22a) were the first to report that both control of ICP and outcome were improved with the use of barbiturates. Patient age was not specified in this report. In this case series, 25 patients with ICP >40 mm

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Kasoff et al. (4), 1988	Case series of 21 children with severe TBI; 11 treated with pentobarbital for intractable ICP. Invasive hemodynamic monitoring used.	III	Children receiving high-dose barbiturates had decreased cardiac index and lower systemic vascular resistance; 91% required dopamine to maintain hemodynamic stability.
Pittman et al. (23), 1989	Case series of 27 children who received pentobarbital for ICP >20 mm Hg despite conventional care.	III	Fourteen of 27 achieved ICP <20 mm Hg with addition of pentobarbital. Seven of 27 experienced persistently elevated ICP, and three of those seven made good ultimate recovery.

TBI, traumatic brain injury; ICP, intracranial pressure.

Hg were treated with high-dose pentobarbital. When ICP was controlled, mortality rate was significantly reduced compared with patients with persistently elevated ICP (21% vs. 83%).

Kasoff et al. (4) reported a case series of 25 children with severe TBI. ICP was monitored in all patients, and surgically correctable lesions were treated with immediate operation. Pentobarbital was administered if ICP remained >20 mm Hg despite hyperventilation to $Paco_2$ 25–30 torr and administration of dexamethasone and mannitol. Each patient (n = 11) who received pentobarbital was monitored with a pulmonary artery catheter. The clinical goals were to maintain ICP <20 mm Hg, cerebral perfusion pressure (CPP) >40 mm Hg, and hemodynamic stability. Ten of 11 children (91%) who received barbiturates required dopamine to maintain CPP compared with 11% of children who did not receive barbiturates. The authors state that all children who received barbiturates had diminished cardiac output and systemic vascular resistance. Nine of the children experienced hypotensive episodes despite intensive monitoring, fluid resuscitation, and dopamine infusions. Thirty-seven percent of the patients died. The specific effects of barbiturates on ICP and CPP were not reported.

Pittman et al. (23) reported a case series of 27 children with severe TBI who received pentobarbital for ICP >30 mm Hg if the intracranial hypertension failed to respond to other treatment modalities. Fourteen (52%) achieved ICP <20 mm Hg after addition of barbiturates. Six (22%) died within 48 hrs despite therapy, and seven had sustained elevation of ICP >35 mm Hg and reduction of CPP (<50 mm Hg) for several hours. No conclusions can be drawn from this study regarding the effect of pentobarbital-related reduction of intracranial hypertension on neurologic outcome. Three of seven patients with sustained elevation of ICP made good recoveries. The authors suggested that barbiturates may have a ben-

eficial effect on outcome even when refractory ICP is not controlled.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

Eisenberg et al. (24) reported a multiple-center randomized clinical trial of high-dose barbiturates in severely head-injured patients with intractable ICP elevations. Patients were between the ages of 15 and 50 yrs. Information on children was not reported separately. This study is considered the best evidence for the use of high-dose barbiturates in adults with uncontrolled ICP. It is the primary study on which the adult guidelines for use of high-dose barbiturates are based (1).

Patients were randomly assigned to barbiturate therapy, whereas the control subjects continued to receive conventional therapies of hyperventilation, muscle relaxation, sedation, mannitol, and ventricular drainage (when possible). Successful control of ICP was the primary outcome variable. Patients in the control group could cross over to the barbiturate treatment group. Thirty-two percent of patients randomized to barbiturate therapy had control of ICP. ICP control was almost twice as likely to be achieved in barbiturate-treated patients compared with the conventional treatment group. The likelihood of survival among barbiturate responders at 1 month after injury was 92% compared with 17% among nonresponders. The primary cardiovascular complication was hypotension.

Therapeutic Regimens

A number of therapeutic regimens have been reported. Eisenberg et al. (24) used the following protocol for pentobarbital.

Loading dose: 10 mg/kg over 30 mins
Then 5 mg/kg every hour for three doses
Maintenance: 1 mg·kg^{-1}·hr^{-1}

Nordby and Nesbakken (25) reported on the use of thiopental in children and adults with severe TBI and used the following dosing regimen.

Loading dose 10–20 mg/kg
Maintenance: 3–5 ·kg^{-1}·hr^{-1}
Doses of thiopental were reduced if blood pressure decreased or ICP was <25 mm Hg.

Although the duration and optimal method to discontinue high-dose barbiturate administration have not been studied, often clinicians seek a period of 24 hrs during which there is good ICP control and no dangerous elevations before beginning to taper off the barbiturate infusion (26).

V. SUMMARY

Small studies of high-dose barbiturate therapy suggest that barbiturates are effective in lowering ICP in selected cases of refractory intracranial hypertension in children with severe TBI. However, studies on the effect of barbiturate therapy for uncontrolled ICP have not evaluated neurologic outcome. Use of barbiturates is associated with myocardial depression, increased risk of hypotension, and need for blood pressure support with intravascular fluids and inotropic infusions. Studies have not evaluated the effect of age on the risk of hemodynamic compromise during high-dose barbiturate therapy. The potential complications of high-dose barbiturate therapy in infants and children with severe TBI mandate that its use be limited to critical care providers and that appropriate systemic monitoring be used to avoid and rapidly treat hemodynamic instability.

There is no evidence to support use of barbiturates for the prophylactic neuroprotective effects or prevention of the development of intracranial hypertension in children with severe TBI.

*S*mall studies of high-dose barbiturate therapy suggest that barbiturates are effective in lowering intracranial pressure in selected cases of refractory intracranial hypertension in children with severe traumatic brain injury.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Clearly, a study of high-dose barbiturates for intractable ICP after severe TBI in children is needed to determine whether they improve outcome.
- The effect of barbiturate therapy in cases of diffuse cerebral swelling in children should be evaluated. Furthermore, no studies have reported the efficacy of high-dose barbiturates for intractable ICP in infants or after injury due to abusive head trauma.
- Age dependence of the deleterious hemodynamic effects of barbiturates deserves further study. Prolonged inhibition of synaptic activity in the developing brain during infancy has been shown to have deleterious effects in recent studies in laboratory models of brain injury (27).
- The effects of barbiturates in infants with severe TBI requires study.

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See APPENDIX on Next Page

APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 13. Barbituates

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. intracranial pressure/or "intracranial pressure" .mp.
6. intracranial hypertension/or "intracranial hypertension" .mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 14. The role of temperature control following severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Extrapolated from the adult data, hyperthermia should be avoided in children with severe traumatic brain injury (TBI).

Despite the lack of clinical data in children, hypothermia may be considered in the setting of refractory intracranial hypertension.

II. OVERVIEW

Posttraumatic hyperthermia is classified as a core body temperature >38.5°C, whereas hypothermia is classified as temperature <35°C. At present, the data in the basic science literature on adult animal models indicate that hyperthermia contributes to greater posttraumatic damage by increasing the acute pathophysiologic response following injury, through a multitude of mechanisms. The rationale for avoidance of hyperthermia and for use of therapeutic hypothermia is to lessen the effect that temperature may have on these mechanisms of secondary injury by decreasing cerebral metabolism, inflammation, lipid peroxidation, excitotoxicity, cell death, and acute seizures. Based on experimental studies in animal models and clinical studies in adults (1) in which hyperthermia was correlated with poor outcome, it has been recommended that hyperthermia following TBI in children should be avoided. There also may be a role for therapeutic hypothermia in reducing intracranial hypertension in severe pediatric TBI. Evidence in both the pediatric and adult literature is evaluated.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 28 potentially relevant studies, two were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

There was one retrospective study from the 1950s by Hendrick (2) indicating that moderate hypothermia (32–33°C) was effective in the treatment of children following severe TBI. This initial investigation was of 18 children with severe TBI (Glasgow Coma Scale score = 4) who presented with decerebrate posturing. There were ten long-term survivors with only one severely impaired. Hendrick concluded that systemic cooling following injury was a "useful adjunct" and could improve outcome in children after TBI. Since that time, there has been a lack of subsequent randomized or other trials to further evaluate this preliminary finding.

In 1973, Gruszhiewicz et al. (3) conducted a prospective, randomized study of 20 children <16 yrs of age who suffered a severe TBI, presenting with a clinical exam of decerebrate rigidity (Glasgow Coma Scale = 4). The children were randomized to one of two groups: hypothermia vs. hypothermia combined with dexamethasone (2 mg twice daily). There was no normothermic group. Nineteen of these 20 patients were hyperthermic at presentation and suffered various mechanisms of injury. Outcome was determined by duration of coma and time until "recovery," although the length of follow-up was <7 months in all instances. Although no statistical analysis was performed, the authors described similar duration of coma and neurologic recovery for the two groups. Surprisingly, 19 patients survived.

Since 1973, no further studies have evaluated the specific efficacy of hypothermia following head injury from which results could be gleaned for pediatric patients. No other studies compared temperature control (e.g., hypothermia with normothermia or hyperthermia) as it relates to outcome. In all other studies, either only adults were studied, or results for children and adults were so confounded that no conclusions can be drawn specifically for pediatric cases. Thus, only two studies met the criteria for inclusion in this chapter.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

There was no section on temperature regulation in the adult guidelines (4) and there has not been an evidence report on this topic in adults. However, a number of studies have assessed the efficacy of therapeutic hypothermia following severe TBI in adults.

The induction of hypothermia clinically to treat patients with TBI was originally reported >50 yrs ago (2), but use of therapeutic hypothermia did not become established because early studies lacked modern scientific methods and adequate outcome measures. Renewed interest in moderate hypothermia after severe TBI did not occur until the early 1990s, when preliminary data from single-center clinical trials were published in adults. Shiozaki et al. (5) used therapeutic moderate hypothermia to 34°C for ≥2 days in a group of severe TBI patients who had intracranial hypertension and were refractory to barbiturate therapy. They found an improvement in cerebral perfusion pressure, compared with normothermic patients, which was sustained during and after rewarming. Marion et al. (6) reported that moderate hypothermia in adult patients with severe TBI reduced intracranial pressure and showed a trend

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Gruszhiewicz et al. (3), 1973	Uncontrolled case series of 20 patients treated with hypothermia vs. hypothermia plus glucocorticoids/steroids (dexamethasone, 2 mg twice daily). Outcome was determined by duration of coma and time to recovery. No long-term outcome cited.	III	No difference in outcome with the addition of steroids to hypothermia. No comparisons or analysis with relation to controlled or normothermic patients.
Hendrick (2), 1959	Uncontrolled retrospective case series of 18 children with a severe TBI who presented with decerebrate posturing and were cooled to 32–33°C.	III	Hypothermia is a useful adjunct with the potential for improved outcome in children with severe TBI.

TBI, traumatic brain injury.

toward improved outcome at both 3 and 6 months after injury. Clifton et al. (7) cooled patients to 32–33°C after severe TBI for 48 hrs and similarly reported a trend toward improved outcome. Marion et al. (8) later demonstrated that moderate hypothermia for 24 hrs specifically hastened neurologic recovery in patients who presented with a Glasgow Coma Scale score of 5–7 and that the treated patients tended to have improved overall outcome. Although these single-center studies provided evidence of efficacy, Clifton et al. (9) more recently reported lack of effectiveness in adults in a multiple-center clinical trial of moderate hypothermia following severe TBI. Despite failure to replicate the earlier single-center findings in the larger multiple-center trial, there was a suggestion of improved outcome in those patients who presented as hypothermic and were then kept cool and in the younger age groups within the study (<40 yrs of age). Children (≤16 yrs) were not included in the Clifton et al. (9) study.

V. SUMMARY

There is presently no published support for temperature control or therapeutic hypothermia in pediatric TBI. Based on studies in adults, therapeutic options include the avoidance of hyperthermia and the consideration of hypothermia for refractory intracranial hypertension.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- The effect of temperature control on outcome following pediatric TBI needs to be studied.
- The role of therapeutic hypothermia, both as a neuroprotective measure and for refractory intracranial hypertension, deserves investigation in pediatric TBI. Direct comparisons to other therapies should be conducted.
- Evaluations of therapeutic hypothermia should be age stratified. Additional documentation of the effect of hypothermia and temperature regulation in studies restricted to infants and children is needed.
- In addition, studies will be needed to better understand the effect of temperature regulation on other physiologic variables (e.g., intracranial pressure, cerebral perfusion pressure, cardiac

> *There is presently no published support for temperature control or therapeutic hypothermia in pediatric traumatic brain injury.*

output, and immune status) and how this might affect long-term outcome.

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See APPENDIX on Next Page

APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 14. Temperature Control

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. hypothermia, induced/
6. 4 and 5
7. limit 6 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 15. Surgical treatment of pediatric intracranial hypertension

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Decompressive craniectomy should be considered in pediatric patients with severe traumatic brain injury (TBI), diffuse cerebral swelling, and intracranial hypertension refractory to intensive medical management.

Decompressive craniectomy should be considered in the treatment of severe TBI and medically refractory intracranial hypertension in infants and young children with abusive head trauma.

Decompressive craniectomy may be particularly appropriate in children with severe TBI and refractory intracranial hypertension who have a potentially recoverable brain injury. Decompressive craniectomy appears to be less effective in patients who have experienced extensive secondary brain insults. Patients who experience a secondary deterioration on the Glasgow Coma Scale (GCS) and/or evolving cerebral herniation syndrome within the first 48 hrs after injury may represent a favorable group. Patients with an unimproved GCS of 3 may represent an unfavorable group.

II. OVERVIEW

The Traumatic Coma Data Bank has established the poor prognosis (34% mortality rate, 16% good or moderately disabled) of pediatric and adult patients with severe TBI and diffuse cerebral injury on computed tomography (CT) scan (compressed cisterns, <5 mm midline shift, mass lesion <25 mL) (2, 3). Because maximum postinjury intracranial pressure (ICP) is a leading predictor of outcome in severe TBI, some have advocated the use of decompressive craniectomy to treat medically refractory intracranial hypertension in children (4–7).

The main objective of decompressive craniectomy is to control ICP and thus maintain cerebral perfusion pressure and cerebral oxygenation, as well as prevent herniation, in the face of refractory cerebral swelling. There are a number of surgical interventions for the treatment of refractory intracranial hypertension. This chapter addresses only the use of decompressive craniectomy. Four questions regarding the use of decompressive craniectomy in children are evaluated:

1. Is decompressive craniectomy successful in controlling ICP?
2. Does decompressive craniectomy improve clinical outcomes?
3. What surgical technique is appropriate?
4. Which patients are appropriate candidates for decompressive craniectomy?

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 21 potentially relevant studies, three were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Is Decompressive Craniectomy Successful in Lowering ICP?

The measured value of ICP may be artifactually altered due to the cranial defect in patients who have undergone decompressive craniectomy. However, given that this surgical procedure is generally undertaken with the goal of controlling severe refractory intracranial hypertension, its effect on ICP is of interest. Taylor and colleagues (8) reported a significant reduction in mean ICP after decompressive craniectomy for severe TBI in children (average mean decrease, 9 mm Hg). Hieu and colleagues (9) illustrated graphically the intraoperative and immediate postoperative ICP at the time of decompressive craniectomy in two pediatric patients. Sequential decreases in ICP seen at the point of craniectomy and of duraplasty were sustained in the immediate postoperative period.

Cho and colleagues (10) reported significantly decreased ICP after decompressive craniectomy (preoperative mean, 59 mm Hg; postoperative mean, 12 mm Hg) in 10 children <2 yrs of age with severe TBI and refractory intracranial hypertension from abusive head trauma.

Key Elements from Adult Evidence Relevant to Pediatric TBI

Polin et al. (4) documented a statistically significant decrease in ICP from 32 to 21 mm Hg after decompressive craniectomy in 26 pediatric and adult patients. In their study, ICP after craniectomy was also lower than ICP at an equivalent postinjury interval in a matched control group taken from the Traumatic Coma Data Bank. Kunze and colleagues (6) reported decreased ICP (mean preoperative, 42 mm Hg; mean postoperative, 21 mm Hg) and increased cerebral perfusion pressure in 28 children and adults who underwent decompressive craniectomy to treat severe TBI. Gaab and colleagues (7) illustrated graphically a single "representative" case from their study of 37 pediatric and adult severe TBI patients showing immediate decrease in ICP and increase in GCS after decompressive craniectomy.

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Polin et al. (4), 1997	In a single-center, case-controlled study, 35 severely head-injured patients underwent decompressive craniectomy with pre- and postoperative ICP monitoring and medical management.	III	A significantly increased rate of favorable outcome was seen in surgical patients compared with matched controls. Young age, early operation, and avoidance of ICP >40 mm Hg may improve outcome.
Cho et al. (10), 1995	In a single-center, case-controlled study, 23 severely head-injured children with shaking-impact syndrome underwent either decompressive craniotomy or medical management.	III	Of patients with severe (>30 mm Hg) intracranial hypertension, those undergoing surgery had improved survival and neurological outcomes compared with those undergoing medical therapy alone.
Taylor et al. (8), 2001	In a single-center PRCT, 27 severely head-injured children with intracranial hypertension refractory to medical management and ventricular drainage were randomized to bitemporal decompressive craniectomy vs. no surgery.	III	Decompressive craniectomy significantly lowered mean ICP in the 48 hrs after randomization and resulted in a marginally nonsignificant trend toward improved clinical outcome at 6 mos.

ICP, intracranial pressure; PRCT, prospective, randomized controlled trial.

Does Decompressive Craniectomy Improve Clinical Outcomes?

Three class III studies evaluated outcome after decompressive craniectomy for the treatment of severe TBI in children. Taylor and colleagues (8) performed a single-center, prospective, randomized clinical trial of decompressive craniectomy in the treatment of pediatric patients (age 1–18) with severe TBI and refractory intracranial hypertension (n = 27). These patients were randomized to receive maximal medical therapy and ventricular drainage alone or in addition to decompressive bitemporal craniectomy. Patients in this study who underwent craniectomy had a trend toward better clinical outcome at 6 months after injury (modified Glasgow Outcome Scale [GOS]). Although this study is a prospective, randomized clinical trial, concerns about size and generalizability of the sample limited the evidence to class III with respect to outcome.

Polin et al. (4) reported the outcomes of 35 patients with mean age 18 yrs who underwent bifrontal decompressive craniectomy for severe TBI and medically refractory intracranial hypertension. Favorable outcome (GOS at discharge from rehabilitation) was more frequent in pediatric (44%) than adult (29%) patients. There was no concurrent control group in this study. However, the authors matched control patients from the Traumatic Coma Data Bank to each study patient. They reported a significantly higher rate of favorable outcome in pediatric patients undergoing decompressive craniectomy vs. controls, based on a univariate analysis. This beneficial effect was

also evident in a multivariate analysis restricted to pediatric patients operated on within 48 hrs of injury and without sustained ICP elevation beyond 40 mm Hg. Hieu and colleagues (9) reported good neurologic recovery in two 8-yr-old patients who underwent decompressive craniectomy within 12 hrs of TBI because of severe intracranial hypertension and evolving transtentorial herniation syndrome. Their operative procedure also included the resection of severely contused brain.

Cho and colleagues (10) reported outcomes in 23 children <2 yrs of age treated with medical therapy or medical therapy plus decompressive craniectomy for severe TBI due to abusive head trauma. In this prospective, single-center, case control study, ten patients with severe intracranial hypertension (>30 mm Hg) received medical ICP management plus decompressive craniectomy, whereas seven patients with severe intracranial hypertension and six patients with less severe intracranial hypertension (<30 mm Hg) were treated with medical therapy alone. Patients with severe intracranial hypertension managed with surgery, and patients with less severe intracranial hypertension, had Child Outcome Scores significantly higher than patients with severe intracranial hypertension managed medically. Among children with severe intracranial hypertension, survival was also significantly improved in those children undergoing decompressive surgery. Decompressive craniectomy in this study was generally performed within 24 hrs of injury. A mean of 32 mL of subdural hematoma was also evacuated at the time of decompressive surgery.

Key Elements from Adult Scientific Literature Relevant to Pediatric TBI

Venes and Collins (11) reported a series of 13 severe TBI patients who underwent decompressive craniectomy, including six children. Although the authors suggested that survival in this retrospective, uncontrolled study was increased relative to historical experience, only two patients, including one child, made a significant neurologic recovery. Kunze et al. (6) performed decompressive craniectomy on 28 severe TBI patients with refractory intracranial hypertension and mean age of 22 (range, 8–44). Although statistical analysis was not performed in this uncontrolled study, the descriptive data suggest markedly better GOS in patients ≤30 yrs of age. Guerra et al. (5) prospectively studied the results of decompressive craniectomy in 57 pediatric and adult patients with severe TBI and medically refractory intracranial hypertension. These authors excluded patients with CT demonstration of severe brainstem injury, absent brainstem auditory evoked responses, absence of oscillatory cerebral blood flow on transcranial Doppler ultrasound, initial GCS of 3 without improvement, or bilateral fixed and dilated pupils. Using these exclusion criteria, the authors estimated that only 3% of severely TBI patients presenting to their institution over a 20-yr period were entered into the decompression protocol. Fifty-eight percent of this highly restricted patient population, however, achieved a GOS of 4 or 5. Logistic regression analysis in this study failed to support young age as a predictor of improved outcome.

What Surgical Technique Is Appropriate?

Studies from the CT imaging era have generally recommended unilateral frontal-temporal-parietal decompressive craniectomy for unilateral cerebral swelling or bilateral frontal craniectomy for bilateral cerebral swelling in both children and adults (5–7). The historical literature is cited as a caution against small craniectomies, due to the potential for inadequate relief of intracranial hypertension and for cerebral incarceration and infarction (5, 12). However, one prospective study of decompressive craniectomy in pediatric patients demonstrated a trend toward improved outcome after 4-cm bitemporal craniectomies (8). Most authors describe a combined craniectomy and expansion duraplasty (4–7, 9, 10). Bilateral procedures used by various authors include separate bilateral craniectomies with a strip of intact bone over the sagittal sinus (5, 7) vs. bifrontal craniectomy with section of the anterior falx cerebri at the skull base (4, 11, 13). No studies have evaluated the differential efficacy of these various techniques.

Which Patients Are Appropriate Candidates for Decompressive Craniectomy?

Three studies of outcome in pediatric patients suggest specific criteria for the performance of decompressive craniectomy. After conducting logistic regression analysis of 35 severe TBI patients treated in their institution, Polin and colleagues (4) recommended decompressive craniectomy for pediatric patients with cerebral swelling and medically refractory intracranial hypertension who are within 48 hrs of injury and who have not experienced a sustained ICP elevation >40 mm Hg. They also recommended against decompressive craniectomy for patients with initial and sustained GCS of 3. Taylor et al. (8) recommended decompressive craniectomy for pediatric patients with refractory intracranial hypertension (ICP 20–24 mm Hg for >30 mins, 25–29 for >10 mins, ≥30 for >1 min) or cerebral herniation syndrome on the first day after injury, despite ventricular drainage.

Cho and colleagues (1995) suggested the use of decompressive craniectomy within 24 hrs of injury in children <2 yrs of age with severe TBI and medically re-

fractory intracranial hypertension (>30 mm Hg) from nonaccidental trauma.

Key Elements from Adult Evidence Relevant to Pediatric TBI

Guerra and colleagues (5) recommended decompressive craniectomy for pediatric and adult patients with severe TBI, cerebral swelling on CT imaging, refractory intracranial hypertension, and witnessed deterioration in clinical variables (GCS, neurologic examination), electrophysiological variables (electroencephalogram, somatosensory evoked potentials), and/or transcranial Doppler ultrasound variables (increased pulsatility, decrease in diastolic flow). These authors excluded patients with CT imaging demonstration of severe brainstem injury, absent brainstem auditory evoked responses, absence of oscillatory cerebral blood flow on transcranial Doppler ultrasound, initial GCS of 3 without improvement, and bilateral fixed and dilated pupils.

V. SUMMARY

Decompressive craniectomy for severe TBI and medically refractory intracranial hypertension in children lowers ICP and may improve outcome. Decompressive craniectomy also may be appropriate in young children with severe TBI and refractory intracranial hypertension from abusive head trauma. Insufficient evidence is available to evaluate the efficacy of various described surgical techniques for decompressive craniectomy. Decompressive craniectomy for children with severe TBI and refractory intracranial hypertension may be most appropriate in patients meeting some or all of the following criteria:

1. Diffuse cerebral swelling on cranial CT imaging
2. Within 48 hrs of injury
3. No episodes of sustained ICP >40 mm Hg before surgery
4. GCS >3 at some point subsequent to injury
5. Secondary clinical deterioration
6. Evolving cerebral herniation syndrome

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Randomized controlled trials of the safety and efficacy of decompressive

> *Decompressive craniectomy for severe traumatic brain injury and medically refractory intracranial hypertension in children lowers intracranial pressure and may improve outcome.*

craniectomy in severe pediatric TBI should be undertaken. The only study of this type may have failed to demonstrate a statistically significant benefit of decompression on long-term outcome due to small sample size.

- It may be useful for future studies to compare decompressive craniectomy to other "second-tier" interventions for severe, refractory intracranial hypertension, such as barbiturate therapy, hypothermia, or lumbar CSF drainage.
- The safety and efficacy of decompressive craniectomy for severe TBI in infants and for severe TBI due to abusive head trauma should be further studied.
- Studies of decompressive craniectomy for severe TBI should include careful monitoring of ICP, cerebral perfusion pressure, cerebral blood flow, and other important physiologic variables to correlate alterations in the latter variables with successful clinical outcome. Such data may clarify the pathophysiological variables involved and provide better information about the indications for and appropriate timing of decompressive surgery.
- Studies are needed to evaluate the optimal surgical approach to decompressive craniectomy.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 15. Surgical Treatment

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. exp intracranial hypertension/ or "intracranial hypertension".mp.
6. 4 and 5
7. limit 6 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
8. limit 7 to English language
9. su.fs.
10. drain$.mp.
11. exp cerebrospinal fluid shunts/ or "cerebrospinal fluid shunts".mp.
12. Neurosurgery/ or "neurosurgery".mp.
13. shunt$.mp.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14

Chapter 16. The use of corticosteroids in the treatment of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

1. Standards. There are insufficient data to support a treatment standard for this topic.

2. Guidelines. There are insufficient data to support a treatment guideline for this topic. The use of steroids significantly reduces endogenous cortisol production. The use of steroids may have an associated increased risk of complications of infection in children.

C. Options. The use of steroids is not recommended for improving outcome or reducing intracranial pressure (ICP) in pediatric patients with severe traumatic brain injury (TBI). Despite two class II studies failing to show efficacy, the small sample sizes preclude support for a treatment guideline for this topic.

D. Indications from Adult Guidelines. The majority of available evidence indicates that steroids do not improve outcome or lower ICP in severely head-injured adult patients (1). The routine use of steroids is not recommended for these purposes.

II. OVERVIEW

Corticosteroids have been commonly used in children, for a wide range of neurologic diseases, to reduce edema (due to tumors, infection, inflammation) and to lessen its neurologic effects. The potential of steroid use in adults following TBI was first indicated in literature reporting the benefits of edema reduction and clinical improvement in brain tumor patients. As summarized in the "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1), there is evidence that steroids are useful in reducing cerebral edema, attenuating free radical production, and affording other beneficial effects in experimental models of TBI, but clinical evidence did not support its use. In the adult literature reviewed, corticosteroids did not improve functional outcome or prove useful in reducing ICP in patients with severe TBI. The studies cited in the adult guidelines did not specifically report on the use of corticosteroids in pediatric patients following severe TBI, but there was a suggestion of potential efficacy in younger patients. A specifically pediatric review was necessary to determine whether there is adequate evidence to support recommendations for children.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 45 potentially relevant studies, eight were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

In clinical practice, steroids have been used in an attempt to reduce posttraumatic swelling and improve outcome in both adults and children. The role of steroids remains uncertain in the treatment of TBI, particularly as it relates to the pediatric population.

Cooper et al. (2) performed a prospective, randomized, double-blind clinical trial with adults and children using dexamethasone. There were 76 total patients, ten of whom were ≤10 yrs of age, and 32 who were less ≤20 yrs of age. Only severely injured patients were included, and each of the patients was randomized to one of three groups—placebo, low-dose steroids, and high-dose steroids. The adults were given standard doses, whereas the children were given weight-related doses. Assignment to the groups was randomized on entry into treatment, but there was no stratification by age. Glasgow Outcome Scale (GOS) was assessed at 6 months. The analysis performed was on the relation of treatment to outcome. The authors reported that in older patients there was no difference in outcome with the use of steroids. Because of the small number of children included, no conclusions could be drawn regarding steroid use in pediatric TBI.

Fanconi et al. (3) performed a randomized, prospective clinical trial on 25 pediatric patients using dexamethasone at 1 mg·kg^{-1}·day^{-1} for 3 days (n = 13) and 12 controls treated with an alternate standard regimen. Outcome was determined by 6-month GOS and response by endogenous free cortisol levels. In this study, there was no difference in effect on ICP or cerebral perfusion pressure and no difference in 6-month outcome. There was a statistically significant suppression of cortisol levels up to 6 days posttreatment. As well, there was a significantly increased bacterial infection rate in those patients treated with steroids.

Gobiet (4) reported on a case control series of 205 children: 139 who did not receive steroids, and 66 who did. The intervention was high-dose dexamethasone, although no specific dose was reported. The nonsteroid treatment group was a consecutive sample of 139 patients from the years 1972–1974 who were treated with neither ICP monitoring nor aggressive intensive care unit therapy. The later steroid treatment group (recruited 1974–1975) received ICP monitoring, intensive care unit management, and steroid therapy. There was no length of follow-up reported, but the measures of outcome included mortality rate, length of intubation, ICP, seizures, and scholastic performance. The authors reported that there was decreased mortality rate with the use of steroids but no difference with regard to length of intubation, time of unconsciousness, incidence of seizures, or neurologic outcome. A comparison between the groups in this study is compromised because significant differences in timing and approach may confound many subtle variables of treatment. However, given the lack of differ-

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Cooper et al. (2), 1979	Prospective, double-blind study of 76 patients with severe head injury (42 of whom were <20 yrs of age, ten of whom were <10 yrs of age). The patients were stratified for severity and treated with placebo or weight-related doses in the children. Six-month GOS was then determined.	III	No significant difference in 6-month outcome in the older children and adults. Potentially improved outcome in children <10 yrs of age, although numbers were too small to determine true differences.
Fanconi et al. (3), 1988	Prospective, randomized clinical trial of 25 patients treated with placebo or 1 mg·kg^{-1}·day^{-1} × 3 days. Endogenous free cortisol and 6-month GOS were determined.	II	Steroid treatment resulted in no difference in ICP, CPP, or outcome. Steroid treatment significantly suppressed endogenous free cortisol and increased infection rate.
Gobiet (4), 1977	Retrospective review of 205 children who received "high-dose" dexamethasone vs. no steroids. The early nontreated group was from 1972 to 1974; the treated group was the later, more aggressively treated population with ICP monitors in treatment of intracranial hypertension.	III	No difference in acute variables or outcome, although there was a suggestion of decreased mortality rate in the treated group.

	Group I No ICP Monitoring or Steroids	Group II ICP Monitoring and Steroids
Number	139	66
Died	58	10
% mortality	41.7%	15.8% ($p < .001$)

Reference	Description of Study	Data Class	Conclusion
Gobiet (5), 1977	Retrospective review of 100 patients using no steroids, normal dose steroids, and "high-dose" steroids in differing doses. The different treatment regimens were not specifically delineated, nor was the relationship between the use of other therapies. Only acute measures were performed.	III	There was no difference in outcome. Steroids reduced brain edema, but there were no data confirming this.
Hoppe et al. (6), 1981	Case series of 22 patients maximally treated with a conglomeration of regimens.	III	Younger patients had a better outcome.

Age, yrs	GOS 1–3	GOS 4–5	% Good Outcome
<20	3	19	86
≥20	9	14	61
Total	12	33	

Reference	Description of Study	Data Class	Conclusion
James et al. (7), 1979	Case control study of nine patients. Group 1 received no or low-dose steroids, and group 2 received high-dose steroids. Neurologic exam and 6-month GOS were determined.	III	No improved long-term outcome based on GOS due to low numbers, although reported improved GCS, mean ICP and ICP wave fluctuations, acute neurologic exam, and ICU and hospital course in the acute period.

Group	GOS 1–3	GOS 4–5	% Good Outcome
Group 1, no or low-dose steroids (n = 4)	3	1	25
Group 2, high-dose steroids (n = 5)	0	5	100
Total	3	6	

Table 1. *Continued*

Reference	Description of Study	Data Class	Conclusion
Kloti et al. (8), 1987	Prospective, randomized clinical trial of 24 patients. Group 1 received dexamethasone (1 mg·kg^{-1}·day^{-1}), and group 2 received no steroids. Urinary-free cortisol in the acute period and 6-month GOS were used for outcome.	IIA	There was near complete suppression of endogenous cortisol, and no difference in long-term outcome.

Group	GOS 1–4	GOS 5	% Good Outcome
Group 1, steroids 1 (n = 12)	3	9	75
Group 2, no steroids 2 (n = 12)	4	8	67
Total	7	17	

Reference	Description of Study	Data Class	Conclusion
Kretschmer (9), 1983	Retrospective review of 107 patients, 51 of whom received a loading dose of dexamethasone, 20–25 mg, and then received a dosing based on whether body weight was < or >35 kg (not based on a mg/kg schedule), in conjunction with standard therapy. This series included penetrating injuries, mild to moderate head injuries, as well as differences in severity between treated and nontreated groups.	III	There was lowered mortality rate in the steroid group in patients with intracranial hematomas and severe injuries (GCS 5–7), although the small numbers precluded conclusion of efficacy.

	Intracranial Hematomas	% of Patients	GCS 5–7	% of Patients
Group 1 (steroids)				
Favorable	15	88.2	14	63.6
Unfavorable	2	11.8	8	36.4
Mortality	2	11.8	3	13.6
Group 2 (no steroids)				
Favorable	11	57.8	9	60
Unfavorable	8	42.1	6	40
Mortality	7	36.8	5	33

GOS, Glasgow Outcome Scale; ICP, intracranial pressure; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; ICU, intensive care unit.

ence between the groups on other variables measured, one might fairly conclude that the addition of an aggressive treatment protocol with ICP monitoring may reduce mortality rate.

Gobiet et al. (5) reported on the study of 100 patients, including 40 children, but there was no separate report of results in the pediatric group. The authors reviewed their experience with ICP monitoring, hyperosmolar therapy, and treatment with or without high-dose steroids in two consecutive patient groups. The earlier patients in the series (1973–1974) all had ICP monitoring and a "standard" therapeutic regimen. The later patients (1975) received steroids in addition to the previous therapies. No conclusion for the use of dexamethasone in pediatric TBI can be drawn from this study because the data for children are confounded with adult measures.

Hoppe et al. (6) reported a case series of 22 patients <19 yrs of age who received intensive therapy in a multiple-treatment regimen including steroids, barbiturates, and hyperventilation. The steroid treatment was dexamethasone 120 mg, given at admission, 6 and 72 hrs after injury, combined with 4 mg every 6 hrs. They reported outcomes measured by 3- and 6-month GOS. Their only conclusion with regard to children was that younger patients had better outcomes, but the authors did not report a specific relation of outcome to the use of dexamethasone.

James et al. (7) reported a retrospective case series of nine pediatric patients with severe TBI. Group 1 received no or low-dose steroids (dexamethasone = 0.25 mg·kg^{-1}·day^{-1}), and group 2 received high-dose steroids (1 mg/kg every 6 hrs for two doses and then 1 mg·kg^{-1}·day^{-1}).

The children otherwise received standard treatment for severe TBI. Outcome was determined by their course and length of stay in the intensive care unit and in the hospital and 6-month GOS. The authors concluded that steroids improved Glasgow Coma Scale (GCS) and neurologic exam by 7-days postinjury, shortened intensive care unit and hospital stay, and decreased mean ICP and ICP wave fluctuations. There was no increase in gastrointestinal hemorrhage or in pulmonary infection. There was no significant difference in GOS outcome at 6 months, although group 2 tended to have better outcomes.

Kloti et al. (8) performed a prospective, randomized clinical trial in 24 severely head-injured children. Group 1 received steroids at 1 mg·kg^{-1}·day^{-1}, and group 2 received no steroids. The children were otherwise treated with stan-

> *With the lack of sufficient evidence for beneficial effect and the potential for increased complications and suppression of adrenal production of cortisol, the routine use of steroids is not recommended for children following severe traumatic brain injury.*

dard therapy. In this study, outcome measures included urinary-free cortisol to assess cortisol excretion as well as functional outcome using the 6-month GOS. There was no difference between the two groups with regard to mean ICP stay, duration of intubation, or 6-month GOS. In group 1, there was complete endogenous cortisol suppression. In group 2 patients, free cortisol was increased 20-fold from normal basal conditions, reaching maximum levels at 1–3 days after injury. In addition, 50% of patients in group 1 developed pneumonia compared with only 15% in group 2.

Kretschmer (9) reported a retrospective review of 107 head-injured pediatric patients with a pathologic finding on computed tomography scan, 51 of whom received steroids. Dexamethasone was given as a bolus (20–25 mg) and then as an infusion based on body weight (above or below 35 kg). The patients otherwise received standard treatment for severe TBI. The two groups differed significantly: a) the study included 29 patients with penetrating injuries, 24 of whom were in the no-steroid group; b) for contusive injury, 29 of 42 patients were treated with steroids; c) mild to moderate head injuries (GCS 8–15) were included but not equally distributed in assignment, resulting in different average severity in the treated and nontreated groups (mean GCS of 7.4 vs. 9, respectively). Outcome was measured by the GOS, but length of follow up was not

reported. Although the overall mortality rate between groups did not differ (24% vs. 23%, treated vs. untreated, respectively), the authors concluded that steroid treatment reduced mortality rate in patients with intracranial hematomas (36.8% vs. 11.8%) and in those with initial GCS 5–7 (33% vs. 14%). Dexamethasone, however, was not useful in the most severely injured patients (GCS 3–4), the mild and moderately injured, or those with penetrating injuries. Because the groups were not evenly balanced on mechanism of injury or severity, conclusions on the efficacy of using steroids in pediatric TBI cannot be drawn from this study.

V. SUMMARY

The majority of available evidence indicates that steroids did not improve functional outcome in pediatric patients with severe TBI. A few studies reported beneficial effect on outcome, but they all had design problems, so recommendations for steroid use cannot follow from their results. In addition, there were as many studies that were inconclusive or lacking any evidence of efficacy. A few studies did not show evidence of complications from steroid use, but two others reported significantly increased rates of infection (bacterial infections and pneumonia) and suppression of endogenous cortisol, which further lessens any enthusiasm for the use of this treatment. With the lack of sufficient evidence for beneficial effect and the potential for increased complications and suppression of adrenal production of cortisol, the routine use of steroids is not recommended for children following severe TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Efficacy

Despite the lack of sufficient clinical evidence of efficacy, there may be subgroups of children with severe TBI who might benefit from the use of high-dose steroids in treatment. Examples of candidate conditions are certain types of pathology (like diffuse swelling or intracranial hematomas), different levels of severity (moderately severely injured, GCS 5–7), and age at injury (school-age children). Further experimental and clin-

ical studies that use high-dose steroids with stratification of these variables among the comparison groups will be necessary before recommendations for treatment can be made.

Complications

Future trials also will need to address the issue of complications, specifically infection and gastrointestinal hemorrhage, and whether preventive interventions (e.g., antibiotics and/or H$_2$ blockers) are effective in reducing or eliminating occurrences.

Endogenous Cortisol

There is evidence that endogenous cortisol production is suppressed with the administration of corticosteroids following severe TBI. The significance of the suppression of endogenous cortisol production and its effect on clinical course and outcome, as well as the effect of an increased catabolic response, needs to be answered.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 16. Steroids

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. exp steroids/ or "steroids".mp.
6. glucocorticoics, synthetic/ or "synthetic glucocorticoids".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 17. Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury

A critical pathway, developed by consensus, is presented in Figures 1 and 2. We developed a treatment algorithm for established intracranial hypertension, wherein the order of steps is determined by the risk/benefit ratio of individual treatment maneuvers. The considerations involved are outlined in the chapter specific to each step.

As discussed in the section on intracranial pressure (ICP) treatment threshold, the absolute value defining unacceptable intracranial hypertension is unclear. Although a general threshold of 20 mm Hg has been presented, there will be situations where such pressures are too high as well as instances where higher ICP values are acceptable. These considerations are relevant to the decision to pursue any step in the escalated treatment of ICP.

This critical pathway is a committee consensus and, therefore, must be viewed as class III ("expert opinion") evidence. As such, it should be interpreted as a framework that may be useful in guiding an approach to treating intracranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps.

This algorithm applies to severe traumatic brain injury. The decision to monitor ICP and apply this algorithm to children or infants with lesser degrees of brain injury is left to the physician.

Critical Pathway

The most fundamental maneuver in managing the pediatric patient with severe traumatic brain injury, outside of the surgical evacuation of intracranial mass lesions, is the insertion of an ICP monitor. Once this has been accomplished, treatment can be directed at controlling ICP and cerebral perfusion pressure (CPP). A number of general maneuvers may be applied to this group of patients early during their treatment, including control of fever, avoidance of jugular venous outflow obstruction, and maintenance of adequate arterial oxygenation. The initial $Paco_2$ should be maintained at the low end of eucapnia (35 mm Hg). In addition, regardless of the presence or absence of intracranial hypertension, CPP should be maintained. The exact value to be targeted should be predicated on age and may be modified by advanced cerebral physiologic monitoring.

When intracranial hypertension occurs, the adequacy of sedation and analgesia should be checked and augmented as needed. In euvolemic patients, the head of the bed may be elevated to approximately 30° and the response of ICP and CPP monitored for efficacy. The addition of neuromuscular blockade to the treatment regimen also may be considered at this point.

If ICP remains elevated despite adequate sedation, analgesia, and elevation of the head of the bed (with or without neuromuscular blockade), the initial ICP-specific therapeutic intervention should be CSF drainage when ventricular access is available. Should an ICP monitor lacking the capability of CSF drainage have been placed, consideration should be given to obtaining ventricular access.

If CSF drainage is ineffective in controlling ICP or is not available, hyperosmolar therapy should be considered. There is insufficient evidence to support prioritizing the use of mannitol vs. hypertonic saline as a first choice. The patient's volume status should be closely observed during mannitol administration, and the upper limits of 320 mOsm/L for mannitol and 360 mOsm/L for hypertonic saline should be observed. If hyperosmolar therapy proves ineffective, the level of ventilation may be increased to obtain $Paco_2$ levels of 30–35 mm Hg. Measurement of cerebral blood flow, jugular venous saturation, or tissue oxygen tension should be considered when hyperventilation is increased.

At all times during the treatment of intracranial hypertension, the possibility that a surgical mass or an unexpected intracranial lesion may have developed should be considered. Therefore, under conditions of intractability or loss of ICP control or when second-tier therapy is being contemplated, clinicians should consider repeating a computed tomography scan.

For intracranial hypertension refractory to the previously described techniques, second-tier therapies should be considered when the physician believes that the patient may benefit if ICP control can be accomplished. Second-tier therapy includes ICP-lowering treatment modalities that have been demonstrated to improve outcome at some level of evidence but that have not been subjected to trials comparing them to alternate second-tier treatments to establish relative risk/benefit ratios. Details of the literature addressing the various second-tier therapies presented here are found in other chapters. Some considerations relevant to differentiating between these differing second-tier maneuvers are contained in the algorithm. The precise indications for selecting and applying second-tier therapies in an individual patient are left to the discretion of the managing physician.
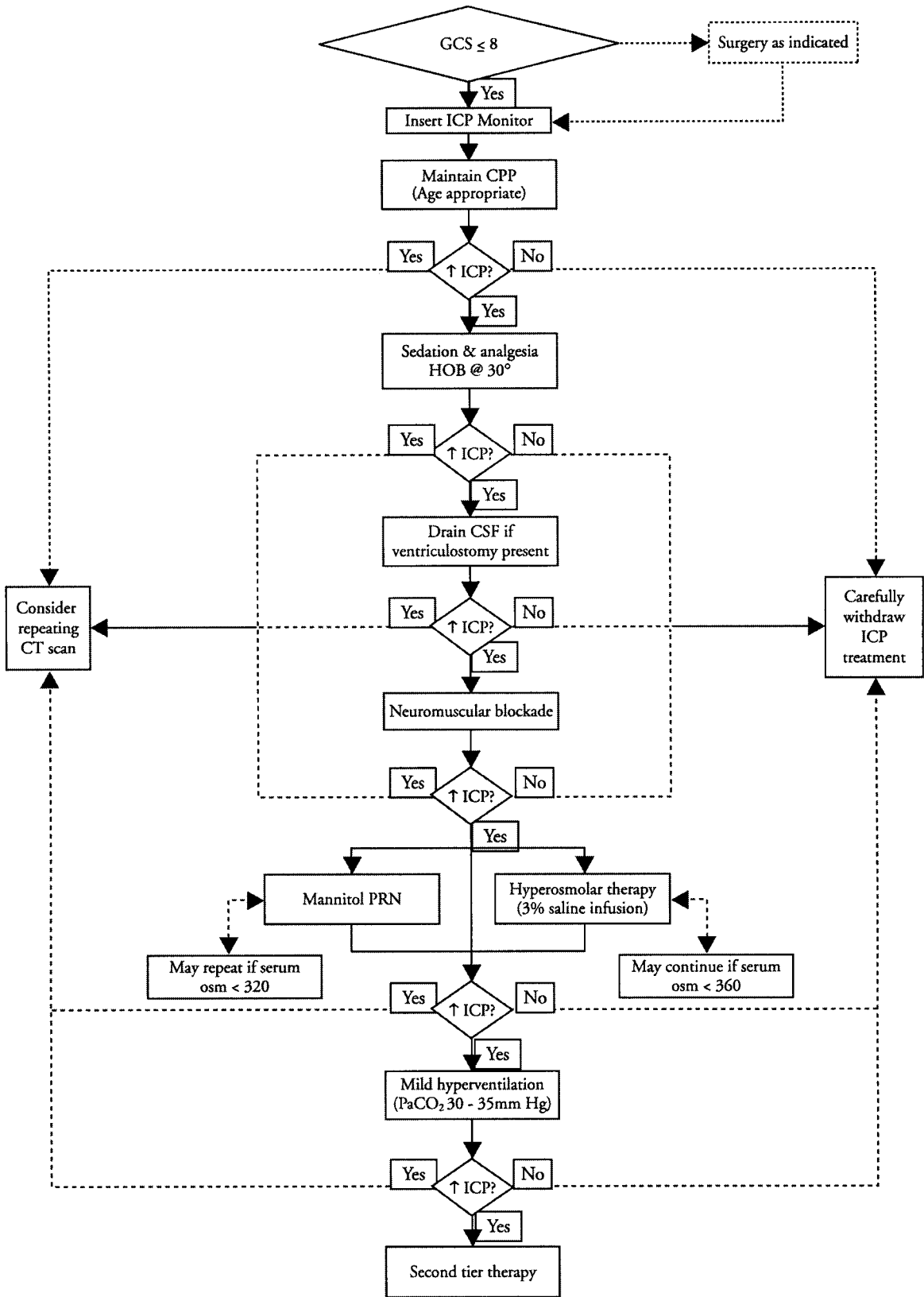
Figure 1. First tier. *GCS,* Glasgow Coma Scale; *ICP,* intracranial pressure; *CPP,* cerebral perfusion pressure; *HOB,* head of bed; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *PRN,* as needed.
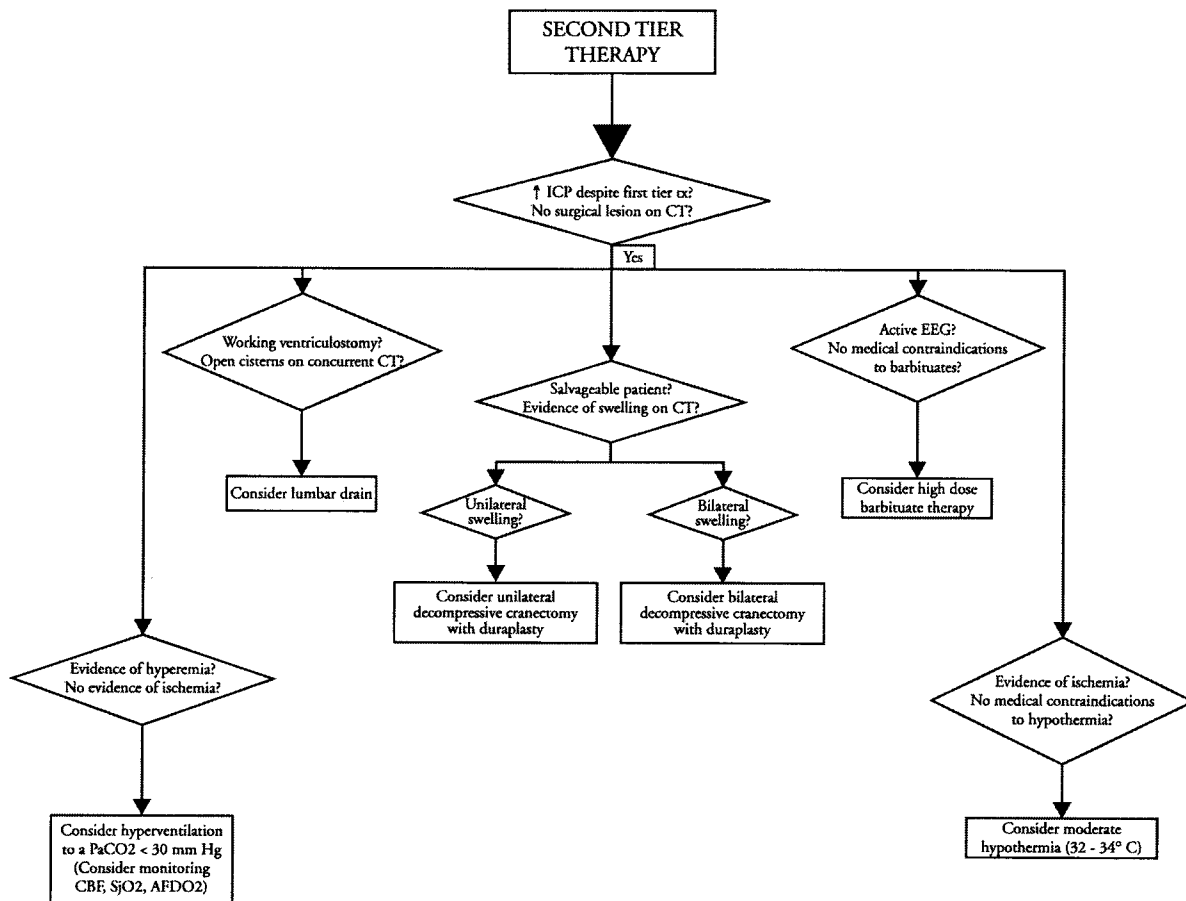
Figure 2. Second tier. *ICP*, intracranial pressure; *CT*, computed tomography; *EEG*, electroencephalogram; *CBF*, cerebral blood flow; *SjO2*, jugular venous oxygen saturation; *AJDO2*, arterial-jugular venous difference in oxygen content.

Chapter 18. Nutritional support

I. RECOMMENDATION

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. Replace 130–160% of resting metabolism expenditure after traumatic brain injury (TBI) in pediatric patients. Weight-specific resting metabolic expenditure guidelines can be found in Talbot's tables (1).

Based on the adult guidelines, nutritional support should begin by 72 hrs with full replacement by 7 days.

D. Indications from Adult Guidelines. At a guideline level, replace 140% of resting metabolism expenditure in nonparalyzed patients and 100% of resting metabolism expenditure in paralyzed patients, by using enteral or parenteral formulas containing ≥15% of calories as protein by day 7 after injury (2).

At an option level, jejunal feeding by gastrojejunostomy is preferred due to ease of use and avoidance of gastric intolerance.

II. OVERVIEW

The nutritional status of pediatric TBI patients may be critical to the recovery process. The question remains unanswered whether nutritional formulations; glucose metabolism; the amount, type, method, or timing of feeding; or any other specific nutritional intervention influences outcome of pediatric TBI patients. There are only two studies (one class II and one class III evidence) that adequately addressed metabolism in children with a brain injury, and no studies that looked at differences in morbidity or mortality rates (3, 4).

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 35 potentially relevant studies, two were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Two studies (one class II and one class III) addressed hypermetabolism and nutritional support in pediatric TBI (3, 4). Phillips et al. (3) examined energy expenditure, nitrogen excretion, and serum protein levels in pediatric TBI patients with a Glasgow Coma Scale of 3–8. The study included eight adolescents (age 11–17 yrs) and four children (age 2–5 yrs). Eleven sustained a blunt head injury, and one had a penetrating head injury by gunshot. All patients were initially intubated and mechanically ventilated for 5–14 days. No patients received corticosteroids. Four patients received neuromuscular blockade. Seven patients were started on total parental nutrition on days 2–6 after injury, and five were started on enteral nutrition on days 3–12 after injury. The study demonstrated a significant elevation in the mean energy expenditure of approximately 130% above predicted levels for the group as a whole (Harris-Benedict equation). Seventy percent achieved nitrogen balance by 4–14 days. The mean urinary nitrogen excretion was 307 $mg \cdot kg^{-1} \cdot day^{-1}$ for the adolescents (mean nitrogen balance of -13.6) and 160 $mg \cdot kg^{-1} \cdot day^{-1}$ for the children (mean nitrogen balance of -4.1). Mean serum albumin levels decreased slightly (from 2.9 mg/dL down to 2.4 mg/dL) whereas total protein levels increased (from 5.4 mg/dL to 6.0 mg/dL). Weight loss ranged from 2 to 26 lb during the 2-wk period showing, despite aggressive nutritional support, a significant decrease in body weight of 9% for adolescents and 4% for children. The effect of neuromuscular blockade on metabolism was not addressed.

Moore et al. (4) measured the metabolic profiles of 20 severe TBI patients (Glasgow Coma Scale <7). Although they studied both adult and pediatric patients (13 and seven, respectively), the data specific to the pediatric patients were sufficiently reported to allow inclusion as class III evidence. All patients were mechanically ventilated. Two of the patients received corticosteroids. Neuromuscular blockade was not addressed. In all patients, feeding was initiated within 48 hrs of admission to the trauma units. It was difficult to ascertain which patients received total parental nutrition vs. enteral nutrition. In the pediatric group (age 3–16 yrs), the study demonstrated an average of 180% of predicted for oxygen consumption and 173% predicted of resting energy expenditure. The average respiratory quotient was 0.68 for both the whole group and the pediatric subgroup.

Although neither of these studies addressed the effect of nutritional support on outcome, the data demonstrate a sizable increase in energy expenditure. The increase in expenditure was highly variable among patients. These studies suggest an increased need for nutritional support in pediatric TBI patients. Insufficient data prevent thorough comparison between the metabolism in adults and children, but the pediatric findings are similar to those well established in the adult literature.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

Hypermetabolism after TBI has been well documented in the adult literature (2–20). At least 12 class I studies have been completed. Nine class I studies examined the effect of amount of feeding, type of feeding, route of feeding, and corticosteroids on nitrogen balance and serum biochemistries. One class I study examined the effect of insulin growth factor I on the catabolic state and on outcome (21). Two class I studies examined the relation between extent of nutritional replacement and outcome (22, 23).

Data from investigators measuring metabolic expenditure in rested comatose patients with isolated TBI showed a mean increase of approximately 140% of the

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Phillips et al. (3), 1987	Energy expenditure, nitrogen excretion, and serum protein levels in pediatric TBI patients with a GCS of 3–8. Total n = 12 (eight adolescents age 11–17 yrs and four children age 2–5 yrs). Eleven blunt head injuries and one GSW. All patients were initially intubated and mechanically ventilated in the emergency department and continued for 5–14 days. No patients received steroids. Four patients were paralyzed with Pavulon. Seven patients were started on TPN on days 2–6 after injury, and five were started on EN on days 3–12 after injury.	II	The mean energy expenditure was approximately 130% above predicted for the whole group. Seventy percent achieved nitrogen balance by 4–14 days. The mean urinary nitrogen excretion was 307 mgdb1·kg^{-1}·day^{-1} for the adolescents (mean nitrogen balance of -13.6) and 160 mg·kg^{-1}·day^{-1} for the children (mean nitrogen balance of -4.1). Mean albumin levels decreased slightly (2.9 mg/dL down to 2.4 mg/dL), whereas total protein levels increased (from 5.4 mg/dL to 6.0 mg/dL). Weight loss ranged from 2 to 26 lb during the 2-wk period showing, despite aggressive nutritional support, a significant decrease in body weight of 9% for adolescents and 4%.
Moore et al. (4), 1989	The metabolic profiles of severe closed TBI patients (GCS <7) were measured. Mixed adult and pediatric, total n = 20 (13 adults, seven children). All patients were mechanically ventilated. Two received steroids. Paralysis was not addressed. In all patients, feeding was initiated within 48 hrs of admission to the trauma units. No distinction between TPN vs. EN.	III	In the pediatric group (age 3–16 yrs), the study demonstrated an average of 180% of predicted for oxygen consumption and 173% predicted of resting energy expenditure. The average respiratory quotient was 0.68 for both the whole group and the pediatric subgroup.

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; GSW, gunshot wound; TPN, total parenteral nutrition; EN, enteral nutrition.

expected metabolic expenditure, with variations from 120 to 250% of that expected. In TBI patients, neuromuscular blockade or barbiturate coma decreased metabolic expenditure from a mean of 160% of the expected to 100–120%. These findings suggest that a major part of the increased metabolic expenditure is related to muscle tone. Even with neuromuscular blockade, energy expenditure remained elevated by 20–30% in some patients (7). In the first 2 wks after injury, energy expenditure seems to increase regardless of neurologic course.

Class I data suggest that when TBI patients are not fed within the first week, mortality rate is increased. Data in critically ill patients without TBI show that a 30% weight loss was associated with an increased mortality rate. After severe TBI, both energy requirements and nitrogen excretion markedly increase. Fasting patients with severe TBI continue to lose 14–25 g N/day (11). Data show that starved TBI patients lose sufficient nitrogen to reduce weight by 15% per week. Given adequate nutritional support, the contribution of protein to consumed calories after TBI increases to levels as high as 30% (24). Class II data show that 100–140% replacement of resting metabolism expenditure with 15–20% nitrogen calories reduces nitrogen loss. The data strongly support full nutritional replacement by the end of the first week after injury.

The optimal method of feeding has not been established. Similarly, it has not been shown that earlier feeding (full feeding before 7 days) improves outcome. Studies showed that, with nearly equivalent quantities of feeding, the mode of administration (total parental nutrition or enteral nutrition) had no effect on neurologic outcome, despite other potential advantages of enteral nutrition (decreased risk of hyperglycemia, lower costs, lower risk of infection). For enteral nutrition, jejunal feeding was better tolerated than gastric feeding (25, 26).

Based on the level of nitrogen wasting documented in TBI patients and the nitrogen sparing effect of feeding, it is a guideline that full nutritional replacement be instituted in the adult TBI patient by day 7. It is suggested that enteral nutrition begin no later than 72 hrs.

Finally, studies of glucose homeostasis suggest that serum glucose control may be critical to limiting secondary neurologic damage. In animal models, hyperglycemia has been shown to worsen ischemic brain injury (27–29). Hyperglycemia was associated with a worse outcome in critically ill patients (30, 31), and tight control of glucose levels (<110) in nondiabetic patients was associated with improved outcome (32). In two studies of severe head injury, hyperglycemia also was associated with worse outcome (33, 34). These studies sug-

gest that serum glucose levels should be tightly controlled in TBI patients.

V. SUMMARY

Due to the limited data that exist on the nutritional requirements of pediatric TBI patients, recommendations can only be made at the option level. Of the two studies addressing pediatric patients, both showed a significant increase in the metabolic rate associated with TBI. These findings are similar to those reported in the adult literature. Without further data, the adult guidelines, adjusted for weight, should be considered when providing nutritional support to pediatric patients with TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Little research has been conducted on nutritional support and its influence on outcome of pediatric TBI. These patients are likely to be highly dependent on precise nutritional interventions tailored to age, weight, body surface area, and other factors.
- Recent studies of glucose homeostasis suggest that glucose control may be critical to secondary damage and neurologic outcome. This topic needs investigation in pediatric patients.
- The issue of hypermetabolism in pediatric TBI needs further confirmation

> *Without further data, the adult guidelines, adjusted for weight, should be considered when providing nutritional support to pediatric patients with traumatic brain injury.*

and clarification. The effects of timing, type, quality, and methodology of nutritional support on the outcome of pediatric patients after TBI need to be investigated.

- Special issues such as vitamin and mineral replacement and other nutritional interventions need to be explored. Authors need to stratify different age groups (infants, toddlers, children, adolescents) in these studies to further delineate developmental differences in nutritional requirements. Without further data, the adult guidelines, adjusted for weight, should be considered when providing nutritional support to pediatric patients with traumatic brain injury.

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See APPENDIX on Next Page

APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 18. Nutrition

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. exp parenteral nutrition/ or "parenteral nutrition".mp.
6. nutritional support/ or "nutritional support".mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)

Chapter 19. The role of anti-seizure prophylaxis following severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. *Standards.* There are insufficient data to support a treatment standard for this topic.

B. *Guidelines.* Prophylactic use of anti-seizure therapy is not recommended for children with severe traumatic brain injury (TBI) for preventing late posttraumatic seizures (PTS).

C. *Options.* Prophylactic anti-seizure therapy may be considered as a treatment option to prevent early PTS in young pediatric patients and infants at high risk for seizures following head injury.

D. *Indications from Adult Guidelines.* Prophylactic use of phenytoin, carbamazepine, or phenobarbital is not recommended for preventing late PTS in adults (1).

Use of phenytoin and carbamazepine has been shown to decrease the risk of early PTS in adults. There is no evidence that outcome is improved. It is a treatment option that anticonvulsants may be used to prevent early PTS in adult patients at high risk for seizures after TBI.

II. OVERVIEW

Infants and small children are known to have lower seizure thresholds (2). Infants can have subtle seizures, making clinical detection difficult (3). An electroencephalogram may be needed to determine whether an infant is experiencing seizures. Treatment of neonatal seizures can be difficult, and single-drug therapy is not effective for the majority of infants (4).

Posttraumatic seizures are classified as early (occurring within 7 days) or late (occurring after 7 days) following injury. As outlined in the adult guidelines, "It is desirable to prevent both early and late PTS; however it is also desirable to avoid neurobehavioral and other side effects of the medications that are ineffective in preventing seizures. Prophylaxis for PTS refers to the practice of administering anticonvulsants to patients following head injury, to prevent seizures. The rationale for routine seizure prophylaxis is as follows. There is a relatively high incidence of PTS in head-injured patients, and there are potential benefits to preventing seizures following head injury" (1).

In the acute period after severe TBI, seizures increase brain metabolic demands, increase intracranial pressure, and may lead to secondary brain injury. The occurrence of late PTS may be associated with accidental injury and psychological consequences. Prevention of early seizures has been suggested to prevent the development of chronic epilepsy (5, 6). On the other hand, anticonvulsants have been associated with adverse side effects such as impaired learning, rashes, Stevens Johnson syndrome, hematic abnormalities, and ataxia, and also with neurobehavioral side effects (5–7). Finally compliance with long-term seizure prophylaxis in children after severe TBI has been poor (7). Critical evaluation of prophylactic anticonvulsant use in children with severe TBI is therefore needed.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 31 potentially relevant studies, three were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

Infants and children are reported to have greater risk of early PTS compared with adults after severe TBI. The reported incidence of early PTS after severe TBI in children varies from approximately 20 to 39% (8–11). Both low Glasgow Coma Scale (GCS) scores (8–11) and young age are associated with increased risk of early PTS (10–13). After adjustment for GCS and duration of coma, children <2 yrs of age have almost a three-fold greater risk of early PTS compared with older children up to 12 yrs of age (odds ratio, 2.96; 95% confidence interval, 1.42–6.21) (9). The incidence of early PTS after abusive head injury has not been reported. Studies report that the majority of early pediatric PTS occurs within the first 24 hrs after injury (10, 11).

The rate of late PTS among children with severe traumatic brain injury ranges from 7 to 12% (7, 8), which is slightly lower than among adults after severe nonpenetrating TBI (9–13%) (5, 8). The relationship of patient age and severity of head injury to the risk of late PTS among children after severe TBI injury has not been reported. Jennet (14) reported that among patients with depressed skull fractures, the incidence of late PTS was 12% in children <5 yrs and 20% in children 5–16 yrs of age. The rate of late PTS among patients >16 yrs of age was 9%. The relation between early PTS in children with severe TBI and late PTS has not been well studied. Among children <3 yrs old who had brain trauma and early PTS, 12% of infants and toddlers experienced late PTS, and risk of late PTS was significantly greater among children <1 yr of age compared with 2- and 3-yr-old children (15).

Studies Regarding Late PTS

Young et al. (7) conducted a randomized, double-blind, placebo-controlled study of late PTS prophylaxis using phenytoin or placebo in 41 children after head trauma. Children were changed to phenobarbital if they developed delayed hypersensitivity to phenytoin. Follow-up was for 18 months. The authors did not report the incidence of early PTS in the study population. The incidence of late PTS in the treated group was 12% vs. 6% in the placebo group. This difference was

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Young et al. (7), 1983	Prospective, randomized, double-blind, placebo-controlled study of 41 patients treated with phenytoin or placebo and evaluated for late PTS. Therapeutic levels were maintained in a minority of patients.	II	Showed no reduction in late PTS. Seizure rates for late PTS were 12% (treated) vs. 6% (placebo) ($P = .25$).
Lewis et al. (10), 1993	Retrospective cohort study of 194 children with head trauma, 31 with severe TBI. Compared PTS in children who received prophylactic phenytoin or no anticonvulsant.	III	Showed reduction in early PTS. Seizure rates were 53% (treated) vs. 15% (no treatment; $P = .04$ one-tailed Fisher's; $P = .057$ two-tailed).
Tilford et al. (17), 2001	Retrospective cohort of 477 children treated at three ICUs with head trauma; 128 had severe TBI. Compared therapies and outcomes by center.	III	Use of prophylactic anticonvulsant varied from 10% to 35% across centers for all children with head trauma. Multivariate analysis of entire cohort showed use of an anti-seizure medication was significantly associated with improved survival (odds ratio, 0.17; 95% confidence interval, 0.04–0.7). Model adjusted for severe TBI, dilated and fixed pupils, serum bicarbonate level, use of vasoactive medications, hyperglycemia, use of a neuromuscular blocking agent, use of an intracranial pressure monitor, and hospital site of care.

PTS, posttraumatic seizure; TBI, traumatic brain injury; ICU, intensive care unit.

not statistically significant. Compliance was poor. By the third month of study, only half of the patients had a level of ≥ 10 µg/mL, and at 1 yr only 10% had the targeted level of 10–20 µg/mL. No patient with a plasma concentration >10 µg/mL had a seizure, and therefore the possibility remains that higher compliance levels might be more effective in preventing late PTS. Because of small sample size and poor compliance with the prescribed anticonvulsant regimen, this study is graded as class II evidence.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

The "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1) reported on six well-controlled studies of prophylaxis for late PTS and concluded that anticonvulsants administered prophylactically do not significantly reduce the incidence of late PTS. The American Academy of Physical Medicine and Rehabilitation published similar conclusions that "antiepileptic drugs are not recommended after 1 wk for preventing *late* posttraumatic seizures in patients without a history of seizures following nonpenetrating traumatic brain injury." (16)

The study of pediatric patients (7), combined with the evidence from adult studies (1), do not support use of prophylactic anti-seizure therapy for prevention of late PTS in children; however, the evidence in children is at the level of a guideline rather than the standard level recommended for adult patients.

Studies Regarding Early PTS

Lewis et al. (10) reported a retrospective cohort study of children treated at a single urban trauma center with head injuries, comparing risk of PTS among children with severe TBI who received prophylactic phenytoin with children with severe TBI who did not receive anticonvulsants. Use of prophylactic phenytoin was determined by the caregivers. Thirty-one children had severe TBI. Patients who received prophylactic phenytoin (n = 17) were compared with children (n = 13) who did not receive prophylactic anti-seizure medications. (One child received multiple anti-seizure medications and was excluded.) Nine (53%) of the children who did not receive prophylactic phenytoin had a PTS, whereas two (15%) of the children who received prophylactic phenytoin had a PTS. Outcome was not reported.

Tilford et al. (17) reported on a retrospective cohort of 477 children treated for head trauma at three pediatric intensive care units. One hundred and twenty-eight had severe TBI. The study evaluated differences in therapies used for head trauma patients at the three intensive care units. Use of anti-seizure medication varied significantly by center, ranging from 10% to 35%. Type of anticonvulsant

medications used was not specified. The overall incidence of PTS was 9%, and the authors did not report the univariate analysis for difference in seizure rate by use of an anticonvulsant or whether all of the PTS occurred in the first week after injury. In a multivariate analysis that included the entire cohort of patients, use of an anti-seizure medication was significantly associated with improved survival (odds ratio, 0.17; 95% confidence interval, 0.04–0.7). The model adjusted for severe TBI (GCS ≤ 8 on admission), dilated and unresponsive pupils, serum bicarbonate level, use of vasoactive medications, hyperglycemia, use of a neuromuscular blocking agent, use of an intracranial pressure monitor, and hospital site of care.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

The "Guidelines for the Management of [Adult] Severe Traumatic Brain Injury" (1) reviewed two well-controlled studies of prophylaxis for early PTS in adults and concluded that anticonvulsants administered prophylactically reduce the incidence of early PTS but do not improve ultimate outcome. Consideration of prophylactic use of anticonvulsants is recommended as a treatment option to prevent early PTS in the adult guidelines (1).

> *Prophylactic anticonvulsant therapy is not recommended to prevent late posttraumatic seizures in children.*

V. SUMMARY

Late PTS

Prophylactic anticonvulsant therapy is not recommended to prevent late PTS in children. If a late PTS occurs, the patient should be managed in accordance with standard approaches to patients with new-onset seizures.

Early PTS

Phenytoin has been shown to reduce the incidence of early PTS in a single study of children with severe TBI (10). Tilford et al. (17) reported an association between use of anticonvulsant therapy and improved survival; however, children with severe TBI were not separately evaluated and the medication used was not specified. Anticonvulsant therapy to prevent the occurrence of early PTS in high-risk children during the first week following severe TBI is recommended as a treatment option.

The scientific evidence suggests that children, especially infants and toddlers, with severe TBI have a greater risk of early PTS than do adults with severe TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Further studies regarding anti-seizure prophylaxis of early PTS after severe TBI in infants and children are needed. A large observational study (17) reported an association between use of anticonvulsant medication and lower mortality rate, raising the possibility that children may benefit more than adults from prophylactic anticonvulsant medications; however, this observation needs to be confirmed.
- Potential differences in effects of anticonvulsant use with age have not been evaluated.
- Further studies regarding risk of both early and late PTS in infants with abusive head trauma as well as mortality rate information are needed. P rophylactic anticonvulsant therapy is not recommended to prevent late posttraumatic seizures in children.

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See APPENDIX on Next Page

APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 19. Seizure Prophylaxis

1. exp craniocerebral trauma/
2. head injur$.tw.
3. brain injur$.tw.
4. 1 or 2 or 3
5. exp seizures/ or "seizures".mp.
6. exp epilepsy/
7. convulsions/ or "convulsions".mp.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
11. exp seizures/dt, pc or exp epilepsy/dt, pc or confulsions/dt, pc
12. 4 and 11
13. limit 12 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
14. exp clinical trials/
15. practice guidelines/ or "practice guidelines".mp.
16. 14 or 15
17. 10 and 16
18. 13 or 17